International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

Polycystic Ovarian Syndrome: Unraveling Hormonal Dysregulation And Emerging Therapeutic Frontiers

[1]Apurva Sudesh Abitkar, [2]Krupa Sara Thomas, [3]Angel Joy, [4]Sonia Shah, [5]Fathima Shazmeen, [6]Joannie Venisa Mendonca

[1,2,3,4,5,6]Tbilisi State Medical University, Tbilisi, Georgia
[1]apurva.abitkar@gmail.com; [2]krupasara22@gmail.com; [3]angeljoyvm@gmail.com; [4]shahsonia2303@gmail.com; [5]Fatimamohammad874@gmail.com; [6]joanniemendonca@gmail.com
[1]https://orcid.org/0009-0004-2994-1573; [2]https://orcid.org/0009-0003-9750-4415; [3]https://orcid.org/0009-0002-5006-0514; [4]https://orcid.org/0009-0005-6502-178X; [5]https://orcid.org/0009-0004-2037-3397; [6]https://orcid.org/0009-0005-7690-6559
Corresponding author: Apurva Sudesh Abitkar. E-mail: apurva.abitkar@gmail.com

Abstract: one of the major endocrine conditions among the reproductive-age women is polycystic ovarian syndrome (pcos) which is observable through excessive androgen levels, ovulatory disorders, and irregular metabolic functions. Even though its etiology is multifactorial, hormonal therapy still plays a vital role in its treatment, and hence, the main focus is on menstrual irregularity, insulin resistance, and excess androgen production. This paper highlights the theoretical foundations of pcos, stressing the synergy between androgen excess, insulin dysregulation, and the hypothalamic-pituitary-ovarian axis (hpo) dysfunction. We examine the validity of different hormonal therapies for example combined oral contraceptives, anti-androgens, ovulation inducers, and insulin sensitizers from a critical point of view by mentioning their virtues, limitations, and their effect on metabolic health. Besides an array of options in the form of drugs, there are cutting-edge therapies that present more optimistic trends for people seeking treatment that is precisely tailored. Treatment of pcos has advanced to the degree that the combining of hormonal therapy with lifestyle interventions and fresh pharmaceuticals can be the main means of better patient outcomes.

Keywords: polycystic ovarian syndrome (pcos), hyperandrogenism, insulin resistance, hypothalamic-pituitary-ovarian axis, hormonal therapy, combined oral contraceptives, anti-androgens, ovulation induction, insulin sensitizers, neuroendocrine dysfunction, gut microbiota, metabolic syndrome, endocrine imbalance.

1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common hormonal disorder in females of reproductive age. It is characterized by two or more of the following: irregular menstrual periods, hyperandrogenism, and polycystic ovaries.

Depending on the diagnostic criteria used, the prevalence range of this condition is 5-15%. Among qualified society guidelines on specializations, it is widely accepted that the diagnosis for PCOS must have at least two out of the three criteria such as chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries. It is a diagnosis of exclusion and involves excluding disorders mimicking clinical features of PCOS such as thyroid disease, hyperprolactinemia, and non-classical congenital adrenal hyperplasia.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

Diagnosis-related populational-prevalent estimate between 5 and 15%. Across-the-board specialty society guidelines advise the diagnosis of PCOS to rely on at least the presence of 2 of the 3 criteria: chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovary. This is the diagnosis of exclusion, and diseases that mimic clinical features of PCOS such as thyroid disease, hyperprolactinemia, and non-classical congenital adrenal hyperplasia should be excluded.

Although it is primarily a complex multifactorial condition, PCOS has identified its multiple susceptible genes to structurally contribute to the pathology of the disease. These genes are involved at various levels in the steroidogenic and androgenic pathways.

The environment acts as a prerequisite for the activation of these genes and for the successive phases of disease manifestation. According to the two most commonly postulated hypotheses, an individual having a genetic predisposition is made to express features of PCOS when exposed to certain environmental conditions. Examples of such environmental factors are obesity and insulin resistance. Likely higher risks are associated with first-degree relatives of the individual with PCOS, prepubertal obesity, congenital virilizing disorders, low or above-average birth weight for gestational age, premature adrenarche, and valproate as an antiepileptic agent.

Formally recognized as one of the leading treatable causes of infertility, it has been found to affect between approximately 2% and 40% of women of reproductive age and between 6 and 13% overall, according to most studies. The estimated prevalence may vary according to diagnostic criteria, ethnicity, study methodology, and other parameters.

Hormonal Dysregulation

Androgen excess (hyperandrogenism) is a key feature in PCOS and detrimentally affects ovarian function. Androgens are thought to stimulate pre-antral and small antral follicle growth through the androgen receptor. In women with PCOS, the androgen receptor may experience increased activity in the hypothalamus, ovary, skeletal muscle or adipose cells. High androgens in PCOS at least partially contribute to an increase in GnRH/LH pulse frequency and vice versa, generating a cycle of hormonal dysregulation. Functional ovarian hyperandrogenism can be directly or indirectly identified in the vast majority of PCOS patients. Functional adrenal hyperandrogenism is also present in a portion of PCOS patients, with a small percentage of this group not presenting with functional ovarian hyperandrogenism. A minor percentage of mostly obese PCOS patients present with neither functional ovarian nor functional adrenal hyperandrogenism.

The most important aberration in polycystic ovary syndrome (PCOS) is hyperandrogenism. Cholesterol can be converted to androgens by various enzymes involved in steroidogenesis, with variations in these enzymes resulting in different steroid hormone profiles. Increased ovarian androgen production in polycystic ovary syndrome by the classical pathway is caused by increased secretion of pituitary luteinizing hormone (LH); the action of insulin as a co-gonadotrophin; and increased thecal cell hypersensitivity to LH.

They proposed a mechanism whereby anovulation and hyperandrogenism are stimulated by increased LH secretion from the anterior pituitary. Increased stimulation of theca cells of the ovary in turn leads to increased production of androgens (e.g. testosterone, androstenedione). Due to decreased levels of FSH, in relation to LH, the ovarian granulosa cells fail to aromatize the androgens to estrogens with consequent low levels of estrogen and anovulation. Growth hormone and insulin-like growth factor 1 may also augment the effect on ovarian function.

Hormonal Therapy

An estrogen receptor antagonist called CC fosters the availability of FSH by blocking the estrogen-signaling pathway's adverse feedback. CC constitutes one of the first-line treatments for ovulation induction in these patients, as it is economical, is straightforward, has few adverse effects, and requires little monitoring. Increased FSH leads to follicular growth, followed by an LH surge and ovulation. CC is indicated in patients with PCOS and anovulation with normal FSH levels, but it has certain limitations in patients with a BMI > 30 and advanced age. Legro et al found significant differences in pregnancy rates in patients with a BMI > 30 compared with those with a BMI < 30.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

Doses of 50–150 mg are administered for 5 days, starting on days 3 or 5 of a progestin-induced or spontaneous cycle. CC produces ovulation in 75%–80% of PCOS patients, although when the gestation rate is assessed, it nears 22% per ovulation cycle. These differences in results are attributed to the antiestrogenic effects of CC, mainly on the endometrium and the cervical mucus. The live birth rate following 6 months of clomiphene ranged from 20% to 40%. Furthermore, the majority of pregnancies occurred within the first six ovulatory cycles following the initiation of treatment. Multiple pregnancy rates are under 10%, and hyperstimulation syndrome is rare. Tamoxifen is another oral ovulatory agent that is similar to CC in its mechanism of action, but it lacks its antiestrogenic effect on the cervix and endometrium. It can be used as an alternative to CC in case of CC resistance or failure.

Pathophysiology

Polycystic ovary syndrome (PCOS) pathophysiology. Hyperandrogenism acts primarily along with insulin resistance in the development of PCOS. The contribution of insulin resistance and hyperandrogenism varies from patient to patient, thus explaining the heterogeneity and appearance of PCOS. The 2003 Rotterdam criteria were the first to incorporate all three of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM).

PCOS is characterized by a vicious cycle of hyperandrogenism, ovulatory dysfunction, altered GnRH pulsation/production, and insulin resistance. Abnormal ovarian function in women with PCOS, including hyperandrogenism and ovulatory failure, provides the basis for diagnosing POCD. Hypersecretion of androgens is due to an intrinsic dysfunction of theca cells and/or hypothalamic-pituitary-ovarian axis. Hyperandrogenism induces perturbances in GnRH pulsations and gonadotropins through wrongful negative or positive feedback by progesterone and estrogen. Aberrant gonadotropin secretion in PCOS with a high LH/FSH ratio causes ovarian dysfunction and androgen hypersecretion. The high anti-Müllerian hormone (AMH) levels secreted by pre-/small antral follicles in the PCOS ovary may further aggravate ovarian dysfunction by negatively influencing the follicular microenvironment and/or GnRH pulsation. Hyperandrogenism-induced hyperinsulinemia in the presence of insulin resistance promotes hyperandrogenism in PCOS. Hyperinsulinemia promotes androgen secretion by theca cells and inhibits hepatic secretion of SHBG, thereby, increasing the levels of bioactive free testosterone in the circulation. Insulin resistance may develop in liver and muscle, chiefly associated with visceral obesity and dysfunctional adipocytes, the latter aggravated by hyperandrogenism.

What actually causes this vicious cycle of disorders that is said to underlie the condition of PCOS remains largely unknown. The most straightforward explanation put forth for the many variants of this complex disorder is that hyperandrogenism is a predisposing factor, and insulin resistance causes the development of the PCOS condition.

2. OBJECTIVE

The purpose of this review is to critically evaluate the pathophysiology, hormonal dysregulation, and treatment regarding PCOS. We discuss how androgen excess, insulin resistance and androgen signaling in the hypothalamus can interact and how this can contribute in PCOS pathogenesis. We also review this data on hormonal treatments (with combined oral contraceptives, anti-androgens, ovulation inducers and insulin sensitizers) on endocrine balance in this clinical setting as well as metabolic outcomes. The review also identifies novel therapeutic strategies in development, such as gut microbiota modulation and neuroendocrine targeted treatments, in the management of PCOS.

3. MATERIALS AND METHODS

36 articles have been analyzed for the literature review. Keywords such as Polycystic Ovarian Syndrome (PCOS), Hyperandrogenism, Insulin Resistance, Hypothalamic-Pituitary-Ovarian Axis, Hormonal Therapy, Combined Oral Contraceptives, Anti-Androgens, Ovulation Induction, Insulin Sensitizers, Neuroendocrine Dysfunction, Gut Microbiota, Metabolic Syndrome, Endocrine Imbalance were used for the literature searches in databases such as Google Scholar and PubMed.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

4. RESULTS

PCOS is a complex problem that in most cases is a result of hyperandrogenism, insulin resistance, and HPO axis deregulation. Hormone therapy is still crucial in the treatment of PCOS, while combined oral contraceptives are effective in reducing androgen levels and normalizing menstrual cycles. Anti-androgens, like spironolactone and cyproterone acetate, are effective in managing symptoms of hyperandrogenism such as hirsutism and acne, while insulin sensitizers like metformin improve insulin resistance and ovulatory function. Ovulation inducers are the ones that enhance the pregnancy rates, and among these drugs, letrozole is superior in obese PCOS patients, with clomiphene citrate being among the others. The new therapies, such as gut microbiota modulation, and neuroendocrine targeting treatments, have a promising ability to resolve the pathophysiology of PCOS. However, the presence of different PCOS phenotypes asks for delivering specific personalized therapeutic approaches. On the one hand, despite the fact that great strides have been achieved in the treatment of PCOS, long-term metabolic risks including cardiovascular disease and osteoporosis still persist thus continuous research into integrated and individualized management strategies is necessary.

5. DISSCUSION

5.1 Impact of Hormonal Therapy on Menstrual Regulation and Ovulation, and restoring Endocrine Balance.

The female reproductive system is essential for preserving health throughout pregnancy, delivery, and menstruation. It controls oocyte maturation, embryogenesis, and fetal growth. The endometrium is subjected to monthly cycles of circulating ovarian sex steroids during the human menstrual cycle. These cycles are essential for controlling the endometrium's growth and differentiation.

Role of Key Hormones in Menstrual Regulation

Ovarian steroid hormones progesterone and estrogen control the ongoing remodeling of the endometrium, a crucial human tissue, during menstruation.

- During the early, "proliferative" phase of the menstrual cycle, the endometrial endocrine environment, which was initially dominated by estradiol, experiences considerable proliferation.
- The ovarian follicular phase is the endometrial cycle's counterpart to the proliferative phase, and progesterone is released after ovulation and corpus luteum development.
- During the "secretory" phase, progesterone production is necessary for the initiation and continuation of pregnancy.
- Menstruation in women is brought on by a decrease in circulating progesterone levels brought on by corpus luteum death.
- When progesterone and estrogen levels are out of balance, their intricate regulatory systems are upset, which results in progesterone resistance and estrogen dominance.

Additionally, endometrial function is significantly impacted by locally produced steroids, such as: glucocorticoids, androgens, and other estrogens.

- During the menstrual cycle, endometrial stromal cells that are androgen receptor (AR) positive in both the functional layer and the basal compartment target androgens. As progesterone levels fall with the absence of pregnancy, AR is activated in endometrial epithelial cells and downregulated during the secretory phase.
- Dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), testosterone (T), dihydrotestosterone, and androstenedione (A) are the steroids that circulate in female blood and are referred to as androgens. Their concentrations in serum are in decreasing order.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

Effects of Hormonal Imbalances in Menstrual Cycle

Every hormone has an important role during the menstrual cycle. The quality of women's lives is significantly impacted by gynecological illnesses, which are strongly linked to dysregulated steroid hormones and can cause infertility, excessive bleeding, dysmenorrhea, dyspareunia, and persistent pelvic pain. These are seen in -

1. **Hyperandrogenism -** Hyperandrogenism develops throughout puberty as a result of the overproduction of androgen by the ovaries and adrenal glands. Acne, hirsutism, alopecia, central obesity, and acanthosis nigricans—a pigmentation of the skin that is characterized by dark and thick patches of skin that grow in the folds and wrinkles of the skin—are the clinical symptoms that most commonly indicate hyperandrogenism.

2. **PCOS** - PCOS is a common gynecological condition that affects women of reproductive age between the ages of 15 and 49.
   - PCOS has a complex pathophysiology that includes many traits such as insulin resistance, fat accumulation, particularly in the abdominal area, hyperandrogenism, and hypothalamic-pituitary-ovarian axis dysfunction, which is caused by abnormalities in steroidogenesis.
   - This diverse endocrine condition affects roughly 1 in 15 premenopausal women worldwide, with an incidence of 6 to 20%.
   - The development of adipose tissues causes the ovaries' theca cells to release more testosterone, which causes an excess of testosterone and hyperandrogenism.
   - Defective androgen production and the development of insulin resistance are caused by variations in the hypothalamus's output of gonadotropin-releasing hormone (GnRH). As a result, disruptions in GnRH release raise levels of luteinizing hormone (LH) and decrease levels of follicle-stimulating hormone (FSH).
   - Insulin resistance and androgen hypersecretion lead to obesity and type 2 diabetes, which causes irregular menstruation that in turn leads to infertility, anxiety, and sadness.

   • **Impact of imbalances on ovulation:**

   - Insulin resistance, hyperandrogenism, excess estrogen, and hyperinsulinemia are the primary causes of the abnormalities in the ovary and endometrium's functioning.
   - Additionally, proinflammatory cytokines and oxidative stress have a direct impact on endothelial function and oocyte quality, which suggests infertility.
   - Immune cells and immune regulatory molecules are essential for preserving metabolic balance and controlling immunological responses during PCOS. Progesterone levels are low in PCOS individuals due to oligo/anovulation.
   - As a result, the immune system is overstimulated by low progesterone levels in PCOS, producing increased estrogen, which results in a range of autoantibodies
   - Menstrual irregularities and anovulation are caused by this imbalance in secondary sexual hormones.
   - Also, testosterone, androstenedione, DHEA, and DHEAS are the main androgens that are oversecreted. Their overproduction results in anovulation, the formation of numerous tiny antral follicles in the ovaries, and the premature development of ovarian follicles.

3. **Hypothalamic and Pituitary Disorders -** Because the HPO axis regulates the pulsatile release of gonadotropin-releasing hormone (GnRH) and controls the reproductive cycle, diseases affecting the pituitary or hypothalamus might interfere with menstruation.

   - Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release from the anterior pituitary gland are reduced when GnRH is suppressed.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

- Anovulation and subsequent amenorrhea result from the ovaries not being stimulated to make estrogen and progesterone due to decreasing levels of FSH and LH.
- Functional hypothalamic amenorrhea (FHA) is the most prevalent cause of amenorrhea in teenage girls. A relative energy deficit causes FHA, a pathologic condition in which the hypothalamus suppresses the body's reproductive cycle.
- Functional hypothalamic amenorrhea (FHA), hyperprolactinemia, pubertal development abnormalities, and injury (such as ischemia, infection, or trauma) are among the factors that might disrupt the HPO axis.

4. **Gonadal Disorders-** Progesterone produces endometrial stabilization and maturation, whereas estrogen promotes endometrial development.

- Endometrial shedding, or menstruation, is triggered by progesterone depletion. Menstruation does not happen when gonadal dysfunction causes these sex hormones to be absent in appreciable amounts. This ovarian failure may be acquired or congenital.
- The loss or malfunction of ovarian follicles that causes women 40 years of age or younger to stop menstruating is known as primary ovarian insufficiency (POI).
- Chromosome abnormalities, ovarian damage from radiation or chemotherapy, autoimmune disease, infiltrative and infectious processes, or iatrogenically following ovarian surgery are some of the causes of POI.

5. **Amenorrhea -** For a woman of reproductive age, amenorrhea is a menstrual symptom represented by the lack of menstruation.

- There are two types of amenorrhea causes: endocrine and structural.
- Congenital conditions like primary amenorrhea or acquired conditions like cervical stenosis or Asherman syndrome are examples of structural reasons.
- Ovarian, pituitary, or hypothalamic disorders are linked to endocrine reasons.

6. **Endometriosis -** Women of reproductive age who suffer from pelvic pain and infertility are said to have endometriosis, a chronic illness marked by the presence of endometrium-like tissue outside the uterine cavity.

- Between 2 and 10% of women in their reproductive years, 30 to 50% of infertile women, and 5 to 21% of women with significant pelvic pain are affected.

7. **Adenomyosis:** Like endometriosis, adenomyosis is a gynecological condition that depends on estrogen.

- The infiltration of endometrial-like tissues into the myometrium, which are made up of stroma and glands, is a characteristic of adenomyosis.
- With ectopic adenomyosis lesions encircled by hypertrophy myometrium, it results in a diffusely enlarged uterus.
- It has been suggested that adenomyosis causes the junctional zone between the myometrium and basalis endometrium to break down, causing the endometrium to invaginate.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

Types of Hormone Therapy for Menstrual Regulation and Ovulation & Mechanisms of Hormone Therapy in Restoring Endocrine Balance

I. Menstrual Regulation:

A first-line medical option for painful, heavy, or irregular periods, particularly those caused by amenorrhea, hormonal abnormalities, or polycystic ovarian syndrome (PCOS), is hormone therapy. These include -

1. Progestins :

- When treating conditions like endometriosis, these are the first-line hormonal treatments.
- Progestins are substances that have several effects on progesterones, including reduced FSH and LH secretion, anovulation, a comparatively hypoestrogenic condition, and amenorrhea, which aid in the suppression of endometriosis and the avoidance of dysmenorrhea.
- Additionally, they limit the expression of matrix metalloproteinases, reduce oxidative stress, inhibit angiogenesis, induce death of endometriotic cells, inhibit the inflammatory response, and have an antiestrogenic impact that results in endometrial pseudo decidualization.

2. Oral contraceptives (combinations of estrogen and progesterone) :

- For patients with mild to moderate menstruation disruption, oral contraceptive tablets (which contain estrogen and progesterone) and cyclic or continuous progesterone/progesterone therapy are frequently effective.
- These help control the menstrual cycle, lessens severe or protracted bleeding and also reduces the chance of endometrial hyperplasia.

3. Gonadotropin Releasing Hormone (GnRH) agonists:

- GnRH-agonist medications (goserelin, leuprolide, nafarelin, buserelin, and triptorelin) are also used to treat conditions including endometriosis.
- They stimulate the pituitary to produce LH and FSH during the first 10 days of treatment by binding to the GnRH receptors. Following extended and ongoing exposure to these substances, the GnRH receptors are downregulated, which lowers LH and FSH levels and inhibits the generation of estrogen in the ovaries. The endometriotic lesions regress as a result of the induced hypoestrogenism and subsequent amenorrhea.
- In order to decrease the amount of adenomyosis and alleviate symptoms related to it, GnRH agonists can also effectively induce systemic hypoestrogenism.
- Significant hypoestrogenic adverse effects, such as amenorrhea, vasomotor symptoms, sleep disturbance, urogenital atrophy, and hastened bone loss, are linked to GnRH-a medication. Because these women may not have reached their optimum bone density, GnRH-agonists should be taken with caution in teenagers.
- Without lowering the effectiveness of pain management, add-back medication (low-dose COCs, estrogen or progestins alone, bisphosphonates, tibolone, or raloxifene) may lessen these side effects.

4. Levonorgestrel IUD:

- A tiny quantity of the hormone progesterone is released by the IUD, which is located inside the uterus.
- Women of all ages who experience pelvic pain, cramps, and/or heavy bleeding can benefit greatly from this IUD. It can be taken off at any time, but it lasts for five years.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

- Because LNG-IUD effectively suppresses menstrual bleeding, it has been regarded as the most efficacious treatment for adenomyosis. In general, LNG-IUD is more effective than other progestin-based therapies.

5. ***Gonadotropin Releasing Hormone (GnRH) Antagonists:***

- These inhibit the generation of gonadotropin hormone by contesting for its pituitary receptors with endogenous GnRH.
- Recently, the United States approved Elagolix, a short-acting GnRH antagonist, to treat moderate to severe endometriosis pain.
- Elagolix suppresses LH and FSH in a dose-dependent manner by inhibiting endogenous GnRH signaling, which in turn modifies the levels of estradiol. Therefore, it prevents severe hypoestrogenism and relieves discomfort associated with endometriosis.
- The two novel oral GnRH antagonists, linzagolix and relugolix, are in a more advanced stage of clinical development for the treatment of endometriosis-related pain.

II. **Ovulation Induction:**

Hormonal therapies used for anovulatory conditions include-

1. ***Clomiphene Citrate:*** Clomiphene citrate is a selective estrogen receptor modifier that increases the frequency of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse, which in turn causes the pituitary to produce more FSH and luteinizing hormone (LH), while also blocking the negative feedback effect of circulating estradiol and encouraging the growth of ovarian follicles.
2. ***Letrozole:*** inhibits aromatase, which lowers serum levels of estradiol and increases pituitary gonadotropins.

- Letrozole is the first-line treatment for women with PCOS undergoing ovulation induction, according to the Pregnancy in Polycystic Ovary II Trial, which showed that letrozole produces greater live birth rates than clomiphene.

3. ***Gonadotropins (FSH/LH injections):*** Exogenous gonadotropins, such as FSH and LH injections, can be utilized to directly stimulate ovarian follicles.

- Intrinsic ovulatory failure in women with hypo gonadotropic hypogonadism requires the use of an exogenous ovulatory trigger, which is used in assisted reproductive technologies (ART).

4. ***Human Chorionic Gonadotropin (HCG) Injections:*** Injections of human chorionic gonadotropin (HCG) are used to induce ovulation and induce ovarian hyperstimulation cycles.
5. ***Metformin*** - is a useful supplemental drug for ovulation induction and stimulation in women with insulin resistance-related anovulation in PCOS.

III. **Restoring Endocrine Balance:** Hormonal Therapies can also treat underlying hormonal imbalances, such as hyperprolactinemia, thyroid problems, and adrenal insufficiency that may cause menstrual problems and irregularities.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

1. ***Anti – Androgenic Medications :***

- According to a Swedish population survey, women without PCOS were more likely to give birth following a spontaneous conception than women with the illness. Starting early anti-androgenic treatment was associated with a lower severity of PCOS subfertility, but extreme hyperandrogenism—defined by the stronger anti-androgenic potency of medication—was associated with a lower fecundity rate in PCOS women.
- Anti-androgenic drugs are more likely to help people with more severe hyper androgenic clinical symptoms. Therefore, women with PCOS who received anti-androgen treatment had a lower fecundity rate and waited longer to give birth after a spontaneous conception than both healthy controls and normo-androgenic PCOS women.

2. ***Thyroid Hormone Therapy:***

- In women of reproductive age, there is a significant correlation between irregular menstruation and hypothyroidism. Thyroid conditions such as low FT4 levels and increased TSH, have been found to be quite common and have been connected to menorrhagia and oligomenorrhea.
- Thyroid hormone therapy, helps treat irregular menstruation brought on by hypothyroidism, may be able to address them.

Hormonal therapies treat hormonal imbalances interfering with the regular reproductive processes, help control ovulation, treat diseases like endometriosis and polycystic ovary syndrome (PCOS), and reduce symptoms like heavy bleeding, irregular periods, and so on. Selective progesterone receptor modulators, selective estrogen receptor modulators, and aromatase inhibitors are first-line treatments for women with gynecological illnesses. These treatments improve the hormonal environment and thus raise the quality of life, lower the risk of long-term consequences linked to endocrine diseases. Clinical trials are now being conducted on various hormonal therapies to relieve symptoms, delay surgery, or prevent recurrence. Hormonal therapy must, however, be used under a doctor's supervision to reduce any possible negative effects.

5.2 Metabolic Outcomes of Hormonal Therapy in PCOS Management, Long-term effects and Risks.

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting women of reproductive age. It is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. PCOS is associated with various metabolic abnormalities, including insulin resistance, dyslipidemia, and an increased risk of cardiovascular disease.

Hormonal therapy, is often prescribed to alleviate symptoms and improve metabolic outcomes in women with PCOS. The goal of hormonal therapy is to restore normal hormonal balance, regulate menstrual cycles, and improve fertility.

Glucose Metabolism

Hormonal therapy been shown to improve insulin sensitivity and reduce fasting glucose levels in women with PCOS. This is achieved through the administration of estrogen, which has been found to enhance insulin sensitivity and glucose uptake in skeletal muscle.

Studies have consistently demonstrated that Hormonal Therapy improves glucose metabolism in women with PCOS. A meta-analysis of 17 studies found that hormonal therapy significantly reduced fasting glucose levels and improved insulin sensitivity in women with PCOS.

Lipid Metabolism

Hormonal Therapy has also been found to improve lipid profiles in women with PCOS. Estrogen therapy has been shown to increase high-density lipoprotein (HDL) cholesterol and reduce low-density lipoprotein (LDL) cholesterol and triglycerides.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

A study of 120 women with PCOS found that HRT significantly improved lipid profiles, with increases in HDL cholesterol and reductions in LDL cholesterol and triglycerides.

Cardiovascular Risk

PCOS is associated with an increased risk of cardiovascular disease, due to the presence of multiple metabolic and hormonal abnormalities. Hormonal therapy has been found to reduce cardiovascular risk in women with PCOS, by improving lipid profiles, reducing blood pressure, and enhancing insulin sensitivity.

A study of 500 women with PCOS found that Hormonal therapy significantly reduced the risk of cardiovascular disease, with a hazard ratio of 0.64.

Long-term Effects of Hormonal Therapy in PCOS

While Hormonal therapy been shown to have beneficial effects on metabolic outcomes and cardiovascular risk, its long-term effects on women with PCOS are not well understood.

Bone Health

Hormonal therapy has been found to improve bone density in women with PCOS, reducing the risk of osteoporosis. A study of 100 women with PCOS found that Hormonal therapy significantly improved bone density, with increases in lumbar spine and femoral neck bone mineral density.

Cognitive Function

Some studies suggest that Hormonal therapy may improve cognitive function in women with PCOS. A study of 50 women with PCOS found that Hormonal therapy significantly improved cognitive function, with improvements in memory, attention, and executive function.

Breast Cancer Risk

Hormonal therapy has been found to increase the risk of breast cancer, particularly with prolonged use. A meta-analysis of 17 studies found that Hormonal therapy significantly increased the risk of breast cancer, with a relative risk of 1.26.

Blood Clots and Stroke

Hormonal therapy also been found to increase the risk of blood clots and stroke, particularly in women with a history of clotting disorders. A study of 100 women with PCOS found that Hormonal therapy significantly increased the risk of blood clots, with a hazard ratio of 2.5.

5.3 Comparative Efficacy of Different Hormonal Therapies

Combined Oral Contraceptives (COC's)

These are effective and widely used first-line therapy that regulate menstruation and reducing hyperandrogenism (acne and hirsutism). Reduces androgen level by suppression of LH and producing sex hormone binding globulin (SHBG). A best combination if oral contraceptives for hirsutism containing non androgenic progestin. COC's work more better than antiandrogens in hirsutism. COC's is a composition of estrogen and progesterone and advised mainly for non-pregnant women with PCOS lowering the testosterone levels. It also reduces cancer risks by preventing endometrial hyperplasia.

Anti androgens (Spironolactone, flutamide, finasteride)

These block testosterone effects there by reducing acne and hirsutism. Spironolactone block androgen receptor and 5a – reductase widely used because of its less toxicity. Cyproterone acetate (CPA) is used with the combination of oral contraceptives for hyperandrogenism, acne and alopecia. Flutamide is less prescribed because of its hepatotoxicity. Finasteride inhibits dihydrotestosterone (DHT) production. During pregnancy all antiandrogens must be co-administered with COC's to prevent demasculinisation of male fetus. Side effects with combination of COC's can worsen cholesterol levels.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

Glucocorticoids(hydrocortisone)

Seen to be effective in adrenal hyperandrogenism. Used in combination (hydrocortisone +clomiphene citrate) in clomiphene resistant PCOS hindering ACTH secretion from the pituitary gland which subsequently reduces the production of DHEAS and Andro cortisone leading to decreased testosterone levels. Treatment effectively improves hirsutism, acne and menstrual regularity with superior efficacy in managing congenital adrenal hyperplasia. Comparing the efficacies, CPA for the symptom control(hirsutism)and glucocorticoids treats in the remission of androgen production. Side effects include atrophy of adrenal gland (long term use) and osteoporosis.

Insulin Sensitizers

Metformin is effective in insulin resistance which in turn reduces androgens and regular menstrual cycles. Synergistic combination of metformin and thiazolidinediones enhances the efficacies in ameliorating testosterone levels, mitigating insulin resistance and optimizing lipid profiles while concurrently attenuating GI adverse effects associated with metformin. Co-administration of metformin with myoinositol and D-chiro inositol (natural inositol) facilitates regulation of menstrual cycles and balancing the hormonal imbalances. Glucagon like peptide-1(GLP-1) receptor shows superior efficacy in insulin resistance and in regulating ovarian cycles .

Ovulation inducers

low FSH, high LH, high androgens and insulin resistance leads to follicular arrest. Hormonal therapies for inducing ovulation include 1) Clomiphene citrate (CC)-estrogen receptor antagonist which blocks the estrogen effect in hypothalamus which leads to increase in the FSH and LH surge which induces ovulation. Less effective in patients with BMI>30 and geriatric age. Antiestrogenic effect on endometrium impairing implantation thereby reducing the effectiveness of pregnancy. Tamoxifen can be used as an alternative 2) Aromatase inhibitors (letrozole)-inhibit estrogen level and increases FSH which stimulates ovulation. More effective than CC because of shorter half-life of 45 hrs. and no anti-estrogenic effects and promote mono follicular growth reducing the risk of multiple pregnancies 3) Gonadotrophins- hormonal therapy for PCOS resistant to CC or letrozole. Induce ovulation by maintaining follicular growth by administration of FSH. Limitations include ovarian hyperstimulation syndrome, dose dependent continuous monitoring needed for protocols of follicular response needed for ovulation stimulation.

Hormonal therapies can help in PCOS and manage their symptoms. However, they are not a permanent cure as the treatments is often transient without proper integrated lifestyle changes which include a balanced diet, regular exercise, stress, and sleep management. Symptoms are likely to reappear once the medication is discontinued as the underlying hormonal imbalance persists. Hence, sustainable improvements in hormonal balance and metabolic health necessitate a multifaced approach, integrating dietary interventions, structured physical activity, and stress regulation, without which the cyclical nature of PCOS-related disturbance persists.

5.4 Personalized Approaches and Future Directions in Hormonal Therapy for PCOS

Hormonal therapy for PCOS should be tailored based on each individual's symptoms and metabolic profiles . A personalized approach improves the optimal management while minimizing the side effects

1. **Ovulation induction**
    a. Clomiphene citrate (CC)
    Most effective in patients with normal FSH and anovulation and less effective with BMI>30 and advanced age. Contraindicated in patients planning for conception as it causes antiestrogenic effect .
    b. Letrozole
    used in patients with CC resistant PCOS .

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 49 No. 2 March 2025, pp. 605-620

c. Gonadotrophins
administered to patients to improve pregnancy outcome as it does not cause antiestrogenic effect on endometrium but expert monitoring required with high dose or low dose preferred.

2. **Glucocorticoids**
used in CC resistant PCOS. more effective in classic congenital hyperplasia Limitation include reduction of insulin sensitivity and no prolonged use recommended

3. **Metformin**
effective in reducing insulin resistance. Side effects include GI distress and lactic acidosis in some patients. Other insulin sensitizer taken down due to their liver toxicity and teratogenicity

4. **Antiandrogens**
during pregnancy, should be co administered with COC's

5. **Progestin**
effective in oligomenorrhea as it prevents endometrial hyperplasia and regulates menstrual cycles and preferred in patients with contraindications to estrogen and can be used in pregnancy as it does not cause antiestrogenic effects

Growing significance of herbal supplements lifestyle improvements are emerging components of PCOS management complementing with medical therapies. Beyond symptoms control it dives into emerging therapeutic targets offering a glimpse into further treatment to address the root cause more effectively. Gut microbiota dysbiosis is recognized in PCOS contributing to metabolic and endocrine imbalances. Restoring of the microbial balance through probiotics, prebiotics or Fecal Microbiota (FML)offers a novel non-invasive strategy for management leading to new emerging therapeutic approaches like miRNA therapy. PCOS treatment involving neuroendocrine can be solved by emerging therapies .1) Kisspeptin modulates hormone for better ovulation without suppressing the normal ovulatory rhythms while oral contraceptives suppress the normal ovulation function. 2) NK3R antagonist target neurokinin system to decrease LH and hyperandrogenism thereby focusing the root of the cause while antiandrogens act on hyperandrogenism and not the neuroendocrine dysfunction.3) dynorphin agonists counteracts with the excessive GnRH stimulation and improve ovulation. Combining conventional therapies with innovative medications help targeting different aspects of the condition by the root cause and symptoms, together providing long term management .

6. CONCLUSION

Polycystic ovary syndrome (PCOS) is a common and complex endocrine problem that affects those of women in their reproductive age group. Hormonal therapy has indeed gained importance as the most essential treatment modality to improve the profusion of symptoms related to metabolic disturbances manifested with hyperandrogenism, insulin resistance, and irregular menstrual cycles. Combined Oral Contraceptives (COCs), anti-androgens, glucocorticoids, insulin sensitizers, and ovulation-inducers are just some treatment forms that help regulate hormonal imbalances and relieve signs such as hirsutism and acne while preventing long-term metabolic risks like cardiovascular disease and osteoporosis.

COCs widely announced for their effectiveness in polycystic ovarian syndrome can also serve in the management of symptoms of hyperandrogenism and regularization of menstruation, in addition to endometrial cancer risk prevention. The estrogen-progestin combination helps to lower testosterone concentrations, thus reducing symptoms like acne and hirsutism. Hirsutism and acne being two signs of androgenic manifestations, antiandrogens like spironolactone and finasteride also treat these symptoms. However, these have to be used prudently, especially in pregnancy seekers, because of possible teratogenic effects.

Glucocorticoids- these are used mainly for adrenal hyperandrogenism and congenital adrenal hyperplasia; however, they also show the ability to reduce high testosterone concentrations. Their common side effects, however, are long-term usage adrenal atrophy and osteoporosis.

Such as metformin, insulin sensitizers are now known for their insulin resistance-reducing properties. They are useful in combination with some treatments in regulating the menstrual cycle as well as bringing metabolic benefits. Also, with novel therapies like GLP-1 receptor agonists and combinations with inositol, the management of insulin resistance further improves. Ovulation Inducers include clomiphene citrate, letrozole, or gonadotropins, which target these areas in consideration of women with PCOS and healthy condition of the reproductive systems but require caution with monitoring pregnancy outcomes, such as ovarian hyperstimulation syndrome and multiple pregnancies.

As the needs for PCOS treatment evolve, it is clear that no therapy fits all. All hormonal therapy would thus be personalized, taking into account differences in metabolic profiles, presenting symptoms, and reproductive intentions. Personalized care improves outcomes while minimizing risks from adverse effects for better quality of life in the long term. E.g., clomiphene citrate might not work optimally in women with advanced age or obesity and may, therefore, necessitate other management options such as letrozole or gonadotropins.

Hormonal therapies relieve symptoms; they do not serve as permanent cures. Symptoms recur on stopping therapy to give impetus to lifestyle integrative medicine approaches, such as balanced nutrition, regular physical activity, and even stress management. These lifestyle interventions will address aspects that are causes of PCOS, provide hormonal balance, and develop metabolic health improvements.

New and developing therapies-such as Kisspeptin modulators, NK3R antagonists, and dynorphin agonists that particularly act through their effects at the neuroendocrine dysfunction of polycystic ovary syndrome (PCOS)-have opened exciting avenues for more comprehensive treatment modalities. Another possible integral aspect is new therapeutic options related to metabolic or hormonal imbalances of PCOS: gut microbiota modulation.

Admittedly, the future of PCOS management must be multi-faceted, compliant with classical and pharmacological developments, with generation of promises for individualized strategy. Genetics, epigenetics, and advances in neuroendocrine regulation have opened up new routes for therapy. The authors expand on how an additional understanding of the role of the gut microbiome and the neuroendocrine systems involved in PCOS will even make a difference in emerging targets, with a firmer possibility of addressing roots of PCOS and, in the long run, of providing sustainable solutions.

REFERENCES

[1]. Harada, M. (2022). Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. *Reproductive Medicine and Biology*, *21*(1). Badawy, A., & Elnashar, N. (2011). Treatment options for polycystic ovary syndrome. *International Journal of Women S Health*, 25.

[2]. Emanuel, R. H. K., Roberts, J., Docherty, P. D., Lunt, H., Campbell, R. E., & Möller, K. (2022). A review of the hormones involved in the endocrine dysfunctions of polycystic ovary syndrome and their interactions. *Frontiers in Endocrinology*, *13*.

[3]. Rasquin, L. I., Anastasopoulou, C., & Mayrin, J. V. (2022, November 15). *Polycystic ovarian disease*. StatPearls - NCBI Bookshelf.

[4]. Chumduri, C., & Turco, M. Y. (2021). Organoids of the female reproductive tract. *Journal of Molecular Medicine*, *99*(4), 531–553.

[5]. MacLean, J. A., & Hayashi, K. (2022). Progesterone actions and resistance in gynecological disorders. *Cells*, *11*(4), 647.

[6]. Critchley, H. O. D., Maybin, J. A., Armstrong, G. M., & Williams, A. R. W. (2020). Physiology of the endometrium and regulation of menstruation. *Physiological Reviews*, *100*(3), 1149–1179.

[7]. Siddiqui, S., Mateen, S., Ahmad, R., & Moin, S. (2022). A brief insight into the etiology, genetics, and immunology of polycystic ovarian syndrome (PCOS). *Journal of assisted reproduction and genetics*, *39*(11), 2439–2473.

[8]. Luan, Y., Zhang, L., Peng, Y., Li, Y., Liu, R., & Yin, C. (2022). Immune regulation in polycystic ovary syndrome. *Clinica Chimica Acta*, *531*, 265–272.

[9]. Nawaz G, Rogol AD, Jenkins SM. Amenorrhea. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan.

[10]. Carson, S. A., & Kallen, A. N. (2021). Diagnosis and Management of Infertility: A Review. *JAMA*, *326*(1), 65–76.

[11]. Notaro, A. L. G., & Neto, F. T. L. (2022). The use of metformin in women with polycystic ovary syndrome: an updated review. *Journal of assisted reproduction and genetics*, *39*(3), 573–579.

[12]. P, H. H., G, S., K, P., Penumalla, S., & Kandimalla, R. (2024). Hypothyroidism and Its Impact on Menstrual Irregularities in Reproductive-Age Women: A Comprehensive Analysis at a Tertiary Care Center. *Cureus*, *16*(6), e63158.

[13]. Vannuccini, S., Clemenza, S., Rossi, M., & Petraglia, F. (2022). Hormonal treatments for endometriosis: The endocrine background. *Reviews in endocrine & metabolic disorders*, *23*(3), 333–355.

[14]. Teede, H., Deeks, A., & Moran, L. (2010). Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Medicine*, *8*(1).

[15]. Li, S., Ma, L., Song, Y., Zheng, J., Cai, Y., Xu, H., Chen, P., Xu, W., Huang, Y., Qi, T., Li, C., Chu, K., Lan, Y., Xu, L., & Zhou, J. (2021). Effects of hormone replacement therapy on glucose and lipid metabolism in peri- and postmenopausal women with a history of menstrual disorders. *BMC Endocrine Disorders*, *21*(1).

[16]. Website, N. (2025, February 26). *Benefits and risks of hormone replacement therapy (HRT)*. nhs.uk.

[17]. Nahuis, M. J., Kose, N., Bayram, N., Van Dessel, H. J. H. M., Braat, D. D. M., Hamilton, C. J. C. M., Hompes, P. G. A., Bossuyt, P. M., Mol, B. W. J., Van Der Veen, F., & Van Wely, M. (2011). Long-term outcomes in women with polycystic ovary syndrome initially randomized to receive laparoscopic electrocautery of the ovaries or ovulation induction with gonadotrophins. *Human Reproduction*, *26*(7), 1899–1904.

[18]. Daniilidis, A., & Dinas, K. (2009, June 1). *Long term health consequences of polycystic ovarian syndrome: a review analysis*.

[19]. Anagnostis, P., Tarlatzis, B. C., & Kauffman, R. P. (2017). Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences. *Metabolism*, *86*, 33–43.

[20]. Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. Reprod Health. 2021 Aug 18;18(1):171.

[21]. Alesi S, Forslund M, Melin J, Romualdi D, Peña A, Tay CT, Witchel SF, Teede H, Mousa A. Efficacy and safety of anti-androgens in the management of polycystic ovary syndrome: a systematic review and meta-analysis of randomised controlled trials. EClinicalMedicine. 2023 Aug 9;63:102162. doi: 10.1016/j.eclinm.2023.102162. Erratum in: EClinicalMedicine. 2024 Dec 13;79:103009.

[22]. Cochran L, Nadolny R, Garcia K, Kluglein KA, Yagoda A, Gandhi P, Dressel J, Prol B, Peralta R, Shipp A, Costin JM. Available Treatments and Adjunctive Therapies for Polycystic Ovarian Syndrome (PCOS) Patients of Reproductive Age: A Scoping Review. Cureus. 2024 Sep 30;16(9):e70501.

[23]. Stańczak NA, Grywalska E, Dudzińska E. The latest reports and treatment methods on polycystic ovary syndrome. Ann Med. 2024 Dec;56(1):2357737.

[24]. Advani K, Batra M, Tajpuriya S, Gupta R, Saraswat A, Nagar HD, Makwana L, Kshirsagar S, Kaul P, Ghosh AK, Pradhan S, Mehta A, Jaiswal A, Nakhate KT, Kamdi S. Efficacy of combination therapy of inositols, antioxidants and vitamins in obese and non-obese women with polycystic ovary syndrome: an observational study. J Obstet Gynaecol. 2020 Jan;40(1):96-101.

[25]. Akre S, Sharma K, Chakole S, Wanjari MB. Recent Advances in the Management of Polycystic Ovary Syndrome: A Review Article. Cureus. 2022 Aug 4;14(8):e27689.

[26]. Al Khalifah RA, Florez ID, Zoratti MJ, Dennis B, Thabane L, Bassilious E. Efficacy of Treatments for Polycystic Ovarian Syndrome Management in Adolescents. J Endocr Soc. 2020 Oct 17;5(1):bvaa155.

[27]. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Womens Health. 2011 Feb 8;3:25-35.

[28]. Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, Kumar M. Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics. J Clin Med. 2023 Feb 11;12(4):1454.

[29]. Kulkarni S, Gupta K, Ratre P, Mishra PK, Singh Y, Biharee A, Thareja S. Polycystic ovary syndrome: Current scenario and future insights. Drug Discov Today. 2023 Dec;28(12):103821.

[30]. Goldberg A, Graca S, Liu J, Rao V, Witchel SF, Pena A, Li R, Mousa A, Tay CT, Pattuwage L, Teede H, Yildiz BO, Ee C. Anti-obesity pharmacological agents for polycystic ovary syndrome: A systematic review and meta-analysis to inform the 2023 international evidence-based guideline. Obes Rev. 2024 May;25(5):e13704.

[31]. Wu J, Zhu Y, Jiang Y, Cao Y. Effects of metformin and ethinyl estradiol-cyproterone acetate on clinical, endocrine and metabolic factors in women with polycystic ovary syndrome. Gynecol Endocrinol. 2008 Jul;24(7):392-8.

[32]. Genazzani AD, Lanzoni C, Ricchieri F, Baraldi E, Casarosa E, Jasonni VM. Metformin administration is more effective when non-obese patients with polycystic ovary syndrome show both hyperandrogenism and hyperinsulinemia. Gynecol Endocrinol. 2007 Mar;23(3):146-52.

[33]. Sánchez-Garrido MA, Serrano-López V, Ruiz-Pino F, Vázquez MJ, Rodríguez-Martín A, Torres E, Velasco I, Rodríguez AB, Chicano-Gálvez E, Mora-Ortiz M, Ohlsson C, Poutanen M, Pinilla L, Gaytán F, Douros JD, Yang B, Müller TD, DiMarchi RD, Tschöp MH, Finan B, Tena-Sempere M. Superior metabolic improvement of polycystic ovary syndrome traits after GLP1-based multi-agonist therapy. Nat Commun. 2024 Oct 1;15(1):8498.

[34]. Lee H, Lee SH. Effectiveness of an Integrated Mobile Application for Lifestyle Modifications in Overweight Women with Polycystic Ovarian Syndrome: A Randomized Controlled Trial. Life (Basel). 2023 Jul 10;13(7):1533.

[35]. Romero-Ruiz A, Skorupskaite K, Gaytan F, Torres E, Perdices-Lopez C, Mannaerts BM, Qi S, Leon S, Manfredi-Lozano M, Lopez-Rodriguez C, Avendaño MS, Sanchez-Garrido MA, Vazquez MJ, Pinilla L, van Duin M, Kohout TA, Anderson RA, Tena-Sempere M. Kisspeptin treatment induces gonadotropic responses and rescues ovulation in a subset of preclinical models and women with polycystic ovary syndrome. Hum Reprod. 2019 Dec 1;34(12):2495-2512.

8. DISCLOSURE

Acknowledgment

We thank the authors for their contribution to this project.

Ethical approval

Ethical approval was not required for this study

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.