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POLYCYSTIC OVARY SYNDROME- A REVIEW

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Abstract: Polycystic ovary syndrome (PCOS) is a widespread reproductive disorder that encompasses many associated health conditions and has an impact on various metabolic processes. Types of PCOS include Insulin resistance PCOS, Inflammatory PCOS, Adrenal PCOS, Post pill PCOS. It has various complications such as Infertility, miscarriage or premature birth, Metabolic syndrome like Hypertension, Dyslipidemia, cardiovascular disease and other includes Type 2 diabetes, sleep apnea, Depression, Anxiety, Abnormal uterine bleeding, Endometrial cancer, Ovarian cancer and breast cancer. There is currently no pharmaceutical treatment for the syndrome, several interventive drugs are utilized to alleviate PCOS's clinical symptoms. Weight and lifestyle (diet, physical activity and behavioural) management are first-line therapy in international evidence-based guidelines for PCOS.

Index Terms **- Infertility, Insulin resistance, Menstrual dysfunction, Hormonal dysregulation.**

INTRODUCTION

The Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in reproductive-aged women [1]. This syndrome is heterogeneous by nature and is characterized by a combination of signs and symptoms of androgen excess and ovarian dysfunction [2]. A majority of women with PCOS have an above-average or high BMI, insulin resistance (IR), menstrual symptoms, and the typical male pattern of baldness, acne, and hirsutism [1].

PCOS affects an estimated 8–13% of reproductive-aged women. Up to 70% of affected women remain undiagnosed or have long delays before the condition is recognized[2].The etiology of PCOS remains unclear; however, most studies suggested that PCOS is an X-linked dominant condition[3].But factors like insulin resistance, hormonal imbalances, genetic factors, obesity, stress and other environmental factors are known to cause PCOS[4]. Polycystic ovary syndrome is recognized as a metabolic disorder, with long term health risks, including hypertension, type 2 diabetes, dyslipidaemia, insulin resistance, and obesity [5].

Stein and Leventhal (Chicago, IL, USA) studied the causes underlying female sterility in the mid-1900s. Stein and Leventhal said that women, who were sterile, which was the same as infertile, had thick body hair and irregular menstrual periods. The 1958 article "The Stein-Leventhal Syndrome: A Curable Form of Sterility" by Irving Freiler Stein Sr. discussed his research on the diagnosis and surgical treatment of Stein-Leventhal syndrome. Women's reproductive health is impacted by Stein-Leventhal syndrome, also referred to as polycystic ovarian syndrome (PCOS). Infertility, an absent menstrual period (amenorrhea), and excessive body hair are all typical signs of PCOS [6].

Over ten follicles are visible on ultrasonography in the ovaries of PCOS patients. It has been suggested that insulin resistance, a potential propensity toward hyperandrogenism, and altered luteinizing hormone (LH) action are factors in the pathophysiology of PCOS [7].

Epidemiology:

The global prevalence of PCOS ranges from 6% to 21%, related to different diagnostic criteria, ethnicities, and regions. There were 1.55 million new instances of PCOS in women of reproductive age worldwide in 2017, and 17.23% of these cases were between the ages of 21–30.In Asia, the age-standardized incidences of PCOS have significantly increased during the last 30 years. PCOS is associated with high risk of metabolic disturbances. Almost 50% of PCOS patients have obesity, 31.1% have impaired glucose tolerance, and 7.5% have type 2 diabetes (T2DM). Compared with non-obese PCOS patients, obese PCOS patients had a higher prevalence of metabolic syndrome (15.9% vs. 47.9%) and insulin resistance (7.1% vs. 27.8%). Under the subgroup analysis, Asian women with PCOS are more vulnerable to metabolic disturbances than other races, with a 5.2-fold increased risk of IGT and a 4.4-fold increased risk of T2DM compared with healthy women.

In summary, PCOS has become more commonplace worldwide over time. Due to the increased likelihood of concurrent metabolic problems, PCOS women's long-term health may be significantly impacted [8].

Types of PCOS:

Insulin resistance PCOS, Inflammatory PCOS, Adrenal PCOS, Post pill PCOS

Etiology:

There are undoubtedly many etiological variables associated with PCOS, even though its exact etiology is unknown or varied.

Insulin Resistance:
Insulin Resistance (IR) is defined as a reduced glucose response to a given amount of insulin. There are several mechanisms leading to IR: Peripheral target tissue resistance, decreased hepatic clearance, or increased pancreatic sensitivity. IR resulting in hyperinsulinemia, which drives excessive ovarian androgen production. Overweight, insulin resistance, and hyperinsulinemia are the key metabolic factors influencing PCOS patients.
The correlation between PCOS and insulin resistance has demonstrated the importance of insulin in particular for females in the reproductive age range. Also, insulin activity in the central nervous system is necessary for ovulation [9].

Hormonal Dysregulation:
Women with PCOS frequently have hormonal imbalances.

- PCOS is associated with elevated levels of testosterone, the primary sex hormone in men. Hyperandrogenism is caused by elevated testosterone levels. The menstrual cycle and ovulation are both regulated by luteinizing hormone (LH). Anovulation and amenorrhea are caused by high LH.
- Follicle stimulating hormone (FSH) controls the process of development, maturation, growth, and reproduction. The smaller follicles experience atresia as a result of the drop in serum FSH levels.
- High level of LH and FSH deficiency may cause loss of menstrual cycles, infertility, decrease in sex drive and vaginal dryness [10].
- Hypoandrogenism is expressed through low levels of sex hormone binding globulin (SHBG).
- A few patients have elevated prolactin levels, which during pregnancy stimulate milk production [4].
- The level of AMH is two to three times higher in women with PCOS than in healthy women, leading to the increased follicular mass or follicular hypersecretion [11].

GeneticFactors:
It has been established that polycystic ovarian syndrome runs in families. Familial occurrence is common, especially when there are first degree relatives [12].
Genes related to biosynthesis, androgen regulation and action (CYP17, CP21, CP11α, 17β-HSD5, SHBG, 11β-HSD, and e H6PD), insulin action and secretion (INSR, VNTR, IRS-1, IRS-2, CAPN10, PPARη, system IGF), gonadotropin secretion and action (follistatin), synthesis and retinoic acid metabolism, and pro-inflammatory genotypes (variants of the TNF-, IL-6) may be involved in the genetic predisposition of PCOS[13].

4 Bisphenyl A (BPA):
One common industrial compound that is used in consumer plastic products, dentistry, and packaging is bisphenyl, which is thought to be a potential cause of PCOS. BPA has role in ovarian dysfunction [10].

Stress and Additional Psychological Conditions:
PCOS often caused by psychological disorders.
Detectable biomarkers of stress that can be found in blood tests are cortisol and DHEA. High levels of these stress hormones reflect the presence of stress in the body whether oxidative, inflammatory, metabolic or emotional stress. Serum Cortisol and DHEA were found to be significantly elevated in PCOS women compared to healthy population [14]. Stress can disrupt the regular menstrual cycle and lead to hormonal changes, such as elevated prolactin and cortisol levels, which can impact menstruation, which typically resumes when the stress diminishes.

Others:
The population can have a significant variation in environmental factors such as food, lifestyle, and physical exercise. The sedentary lifestyle, dietary holidays, skipping workouts or engaging in intense physical activity, as well as contributing factors like drastic weight loss, endocrine system problems, and different ovarian disorders [15].

Diagnosis:
Three organizations have proposed specific criteria for PCOS: the Androgen redundant and PCOS Society; the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM); and the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD)[16].The "Rotterdam Criteria" remains the most commonly used diagnostic tool for PCOS today; its prevalence can reach five times higher than that of the NIH criteria[13].

TABLE 1 Diagnostic Criterion for PCOS

Parameter	NICHD/NIH Criteria (1990)	ESHRE/ASRM Rotterdam Criteria (2003)	Androgen Excess Society (AES) Criteria (2006)
Criteria	Clinical or biochemical Hyperandrogenism	Clinical or biochemical Hyperandrogenism	Clinical or biochemical Hyperandrogenism
	Oligo-ovulation/Anovulation	Oligo-ovulation/Anovulation	Oligo-ovulation/Anovulation
		Polycystic ovaries	Polycystic ovaries
Limitations	Two of two criteria required	Two of three criteria required	All criteria required.

Phenotypes of PCOS:

Four phenotypes of PCOS were identified by the 2012 Evidence-Based Methodology PCOS Workshop, which was sponsored by the National Institutes of Health [17].

TABLE 2 Phenotypes of PCOS

Phenotype A	Full blown PCOS	• Hyperandrogenism • Ovulatory dysfunction • Polycystic ovary morphology
Phenotype B	Non-Polycystic ovary PCOS	• Hyperandrogenism • Ovulatory dysfunction
Phenotype C	Ovulatory PCOS	• Hyperandrogenism • Polycystic ovary morphology
Phenotype D	Non-Hyperandrogenic PCOS	• Ovulatory dysfunction • Polycystic ovary morphology

Pelvic ultrasonography:

Pelvic ultrasonography can also be very beneficial in the evaluation process, but over 20% of "normal" women also have polycystic ovaries, suggesting that the condition is not unique to PCOS. In the ultrasound evaluation, the quantity of follicles and ovary volume are both significant.

- Most frequently used criteria for PCOS are those proposed by Adams et al.: ≥10 cysts, ranging in size from 2 to 8 mm, surrounding a dense core of stroma or dispersed throughout an increased amount of stroma.
- According to Jonard et al., there is also an additional requirement of "increased ovarian area (>5.5cm2) or volume (>11 mL) and/or presence of ≥12 follicles measuring 2 to 9 mm in diameter (mean of both ovaries)."

When it came to PCOS diagnosis, these criteria had 99% specificity and a 75% sensitivity [18].

Testosterone:

- In PCOS, testosterone levels might be normal.
- In PCOS, the majority of testosterone values will be ≤150 ng/dL, or ≤5.2 nmol/L.
- When testosterone levels are greater than 200 ng/dL (6.9 nmol/L), an adrenal or ovarian tumor should be suspected.

Dehydroepiandrosterone-sulfate (DHEA-S):

- DHEA-S levels in PCOS patients may be normal or slightly elevated.
- If DHEA-S is greater than 800 µg/dL (21.7 µmol/L), an adrenal tumor should be suspected.

Prolactin:

- It has been reported that 5% to 30% of PCOS patients have mild hyperprolactinemia. Prolactin typically exceeds the upper limit of normal by only 50%.
- Ultrasonography may reveal polycystic ovaries in patients with prolactinomas.

24-hour urine free cortisol:

- Slight increases are observed in PCOS; values greater than twice the upper limit of normal are more in line with Cushing's syndrome.

Luteinizing hormone/follicle stimulating hormone (LS/FSH) ratio:

- While not very sensitive or specific, a ratio of ≥2.0 is suggestive of PCOS [18].

Anti mullerian hormone (AMH):

- Women with PCOS often have elevated serum AMH levels.
- AMH levels greater than 3.19 ng/mL were substantially linked to PCOS [19].
- Serum AMH levels above normal indicate hyperandrogenic PCOS patients, irrespective of ovulatory or polycystic ovary status [20].

Clinical features:

Menstrual irregularity: Menstrual disturbance is seen about 60-85%, the degree of Ovarian dysfunction, the amount of follicular activity and circulation concentration of estrogen stimulating endometrial development will determine whether women would have Amenorrhea or oligomenorrhea (cycles length more than 35 days) and polymenorrhea (frequent cycles occurring in intervals of< 26 days in length)[21].

Figure 1. Sign and symptoms of PCOS [22]

Hirsutism:
High amounts of Androgens (Hyperandrogenism) influence various aspects of follicular activity. In androgen-sensitive regions, they accelerate the growth, diameter, and melanization of hair by acting through androgen receptors and secretory factors. A modified Ferriman-Galway score is used to assess the degree of hirsutism. This score rates nine different body areas in a range of 1 to 4. If the total score is higher than 6–8, it is significant [23].

Androgenic alopecia:
The cause of female pattern hair loss may not always be androgenic in nature. Female pattern hair loss (FPHL) in women who experience it early is most likely linked to hyperandrogenism. The scalp appears bald because of hormonal changes that turn terminal hair into vellums hair [23].

Acne:
Chronic inflammation of hair follicles resulting in a persistent polymorphic dermatosis. Four pathological events—follicular canal hyperkeratosis, sebaceous hypersecretion, bacterial proliferation, and inflammation—are present in the clinical presentation of acne. An accumulation of fat and overlapping bacterial infection are the results of chronic hyperandrogenism, which raises sebum secretion. In addition to the face, the chest, shoulders, and back may also experience acne lesions [24].

Infertility:
Chronic anovulation is the primary cause of infertility in women with PCOS. Subfertility is associated with the rise in LH plasma levels during the follicular phases of the cycle, which results in the early release of oocytes and the restart of the oocyte's second meiotic division [24].

Obesity:
PCOS and central obesity are commonly linked. A ratio of 0.85 or higher between the waist and hips is considered central obesity. For instance, central obesity is defined as having a waist circumference greater than 34 inches and a hip circumference greater than 40 inches. Central obesity appears primarily in the abdomen. Obesity increases the hyperestrogenic environment in PCOS-affected women by converting adrenal and ovarian androgens to peripheral fat cells that secrete estrone [25].

Virilization:
Virilization is related to hair and may indicate male pattern baldness or alopecia, or the loss of scalp hair. Moreover, virilization may cause changes in voice quality, a rise in muscle mass, clitoris hypertrophy, or even breast atrophy [25].

Acanthosis nigricans:
Acanthosis nigricans (AN) which is characterized by thickening and darkening of the upper layers of skin, which results in velvety appearance. The typical areas which are involved are the posterior neck and axilla [26].

Complications:
Infertility, miscarriage or premature birth, Metabolic syndrome like Hypertension, Dyslipidemia, cardiovascular disease and other includes Type 2 diabetes, sleep apnea, Depression, Anxiety, Abnormal uterine bleeding, Endometrial cancer, Ovarian cancer and breast cancer[27][28].

Pathophysiology:
Because of biochemical disruption that throws off the menstrual cycle, the pituitary gland secretes more LH in PCOS patients. Infertility will result from the absence of developed follicles. Certain follicles may not dissolve; instead, they stay in place and develop into fluid-filled sacs resembling structures called cysts. Increased testosterone production from elevated insulin and LH levels results in hirsutism, acne, and the prevention of ovulation, all of which worsen infertility.

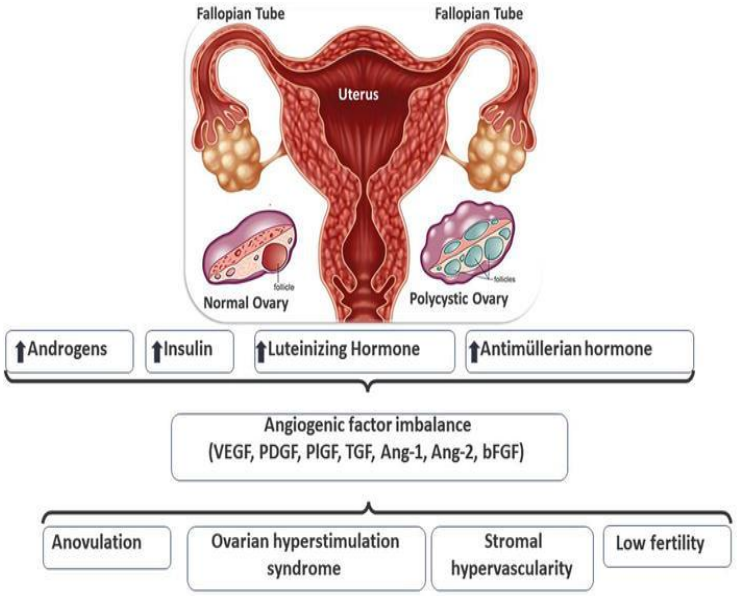

FIGURE 2: Polycystic Ovary Syndrome Pathophysiology [29]

The pathophysiology of PCOS has been explained by a number of theories [30][31]:

1) Distinct malfunction in the action and production of insulin that causes hyperinsulinemia and IR
2) A fundamental neuroendocrine abnormality that causes an increased amplitude and frequency of the LH pulse.
3) A flaw in androgen synthesis that leads to increased androgen production in the ovaries
4) An increase in adrenal androgen synthesis due to a change in cortisol metabolism

Management:

➢ **Pharmacological Therapeutic options for PCOS:**

Although there is currently no pharmaceutical treatment for the syndrome, several interventive drugs are utilized to alleviate PCOS's clinical symptoms [32]. The general state of illness is improved by pharmacological treatments in conjunction with lifestyle modifications. Treatment approaches for ovulatory dysfunction, hyperandrogenism, insulin resistance, and infertility differ depending on the clinical manifestations and underlying etiology [33].

➢ **Goals of treatment includes:**

- rectifying anovulation
- preventing androgens' effects on the targeted tissues,
- Reducing insulin resistance and
- To treat infertility.

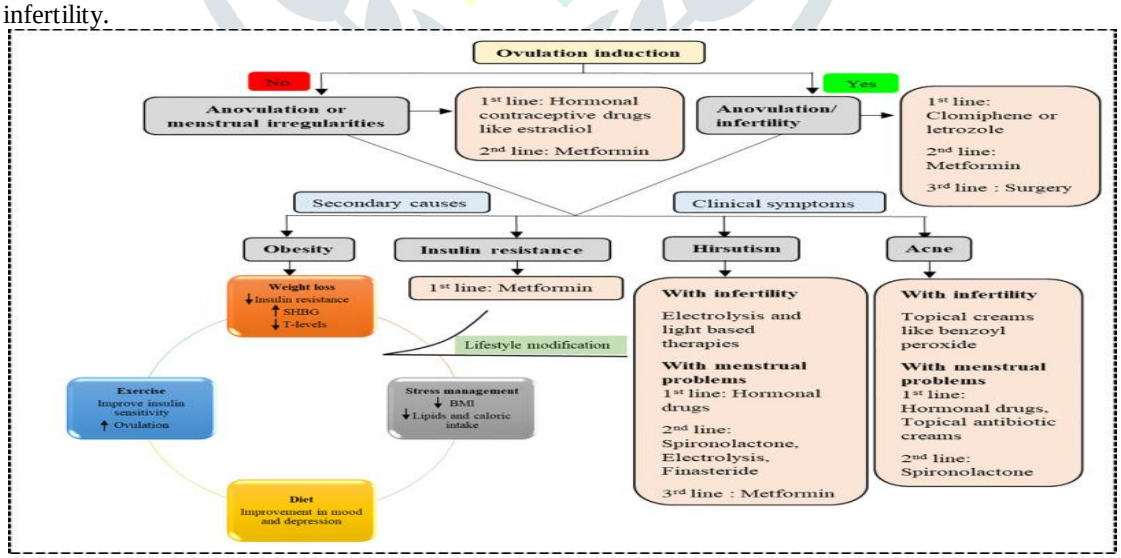

FIGURE 3: Polycystic ovary management protocol stating the treatment options for anovulation and infertility including clinical symptoms [34].

1) Oral contraceptives (OCPs):

Controlling menstruation is the main way that OCs work to treat PCOS. These medications also lower testosterone levels, which reduces acne, hirsutism [35]. The OCPs are divided into progesterone-only and mixed pills that contain progesterone (norethisterone, desogestrel) and estrogen (maximum 50µg dosage of estradiol). For women who experience irregular menstruation and do not want to ovulate, they are the first line of treatment [15]. Through a number of mechanisms, such as increased circulating SHBG levels, decreased ovarian androgen secretion, and pituitary LH secretion, they provide benefits [23].

Although there is a lack of evidence to support particular progestin or estrogen types or dosages, or combinations of COCPs, for the treatment of PCOS in women and adolescents, it is still important to take into account the lowest effective estrogen dose, which is 20 to 30 g of ethinylestradiol.

Contraindications:

Prior to prescribing COCPs, a complete medical history of the patient and her family should be obtained in order to evaluate contraindications such as thromboembolism risk. For PCOS, 35 ug of ethinylestradiol plus cyproterone acetate preparations shouldn't usually be thought of as first line treatment. In adolescents with PCOS, treatment durations longer than 24 months have not been assessed [36].

Some of the more recent OCs, like Bayer'sdrosperenone (e.g., Yaz) and dienogest (e.g., Natazia), contain anti-androgenic progestins. Theoretically, when compared to earlier formulations, these medications are more effective at treating androgenic symptoms. After taking OCs for about six months, women with hirsutism typically experience a clinical improvement. For synergy, these can be taken in conjunction with antiandrogens [37].

2) Anti androgens:

This class of medications, which is recommended as first-line treatment for hirsutism, comprises spironolactone, flutamide, cyproteroneacetate, and finasteride. These medications reduce androgen secretion by inhibiting androgen receptors[15].

Spironolactone is a both a weak androgen receptor antagonist and a mineralocorticoid antagonist, spirolactone has dual actions. Spironolactone also decreases testosterone biosynthesis and the activity of 5-alpha reductase, the enzyme that changes testosterone into the more powerful dihydrotestosterone [38].

Dose: 25-100 mg twice daily [35].

Flutamide:

Nonsteroidal antiandrogen flutamide binds to androgen receptors throughout the body in a competitive manner. By preventing testosterone's stimulating effects, this binding stops the growth of prostate cancer cells. Compared to other agents like finasteride, cyproterone acetate, and spironolactone, flutamide has been shown to be more effective at treating hirsutism's symptomatology, despite carrying a risk of hepatic injury [39].

Cyproterone acetate

Strongly progestogenic, cyproterone acetate is an antiandrogen. Hirsutism and acne are treated with a combination of ethinylestradiol and cyproterone acetate [15].

Finasteride

Another drug that helps control hirsutism and lessen hyperandrogenic symptoms in PCOS patients is finasteride, a 5-alpha reductase inhibitor that prevents it from being converted to DHT [23].

3) Insulin sensitizing agents:

Individuals with PCOS have altered insulin secretion and function. Ovarian activity is regulated by insulin, and high insulin levels can damage ovaries. In reaction to excess insulin, muscle cells release large amounts of androgens, which delays follicular development and causes the polycystic ovarian morphology that is typical of PCOS. Insulin resistance has long been associated with Acanthosis nigricans. Patients with PCOS are more susceptible to long-term health problems like type 2 diabetes and cardiovascular disease due to insulin resistance. Therefore, managing insulin resistance with drugs and changing one's lifestyle is crucial for PCOS treatment [35].

A. Metformin:

This biguanide works by reducing intestinal glucose absorption, blocking hepatic glucose synthesis, and raising insulin sensitivity in peripheral tissues [40]. It is recommended that metformin be started at 500mg of slow release daily and increased gradually over weeks to months to reach 2g of the medication daily [41].

Gastrointestinal symptoms such as nausea, vomiting, anorexia, abdominal pain, and diarrhea are among the side effects of metformin [42].

For PCOS patients who are obese or trying to lose weight, metformin is most likely the first drug of choice. When taking metformin, one can experience a reduction in body mass index (BMI) of 1 to 2 kg per m^2 or lose upto 3 to 4 kg of weight (6 lb, 10 oz to 8 lb, 13 oz) [43].

B. Thiazolidines

Glitazones is the colloquial term for this group. Among its pharmacological ligands for the nuclear receptor peroxisome proliferator activated receptor y (PPARY) are pioglitazone and rosiglitazone. Their effects on hepatic glucose output are minimal, and they enhance the function of insulin in the liver, skeletal muscles, and adipose tissue [23].

TZDs decrease blood levels of androgens by raising insulin sensitivity, which in turn lowers insulin levels. Pioglitazone has an effect on lowering ovulatory dysfunction, hyperandrogenism, and insulin resistance. It raised SHBG levels in PCOS patients while markedly lowering fasting serum insulin and free testosterone levels [44].

C. Inositols

Cells in both humans and plants contain large amounts of the carbocyclic sugar inositols. Nine isomeric forms are known to exist for it, with myoinositol (MI) and d-chiro-inositol (DCI) being the most prevalent variations [44]. One promising therapeutic approach for treating PCOS patients may involve the use of two inositol isomers: myo-inositol (MI) and D-chiro-inositol (DCI). Insulin resistance, serum testosterone levels, and other metabolic syndrome characteristics are improved by inositols. They serve as secondary messengers for insulin and mediate its various actions. MI and DCI, although similar, have distinct roles in the development and management of PCOS. The conversion of MI into an inositol phosphoglycan (IPG) insulin second messenger (MI-IPG) is responsible for the uptake of glucose by cells, while the conversion of DCI into

an IPG insulin second messenger (DCI-IPG) is crucial for the synthesis of glycogen. The amounts of luteinizing hormone (LH), testosterone is decreased by both MI and DCI in PCOS patients [40].
With few safety concerns, MI supplements are typically well-tolerated at the current dose recommendations of 2-4 g/day [44].

D. GLP-1 agonists

One class of antidiabetic medications that mimics the action of incretins is called GLP-1 receptor agonists [40]. An increase in glucose-dependent insulin release, particularly after a meal, is provided by incretins, which are gut hormones that include glucose-dependent unguided polypeptides (GIP) and glucagon-like peptide (GLP1). Incretin-related response A alteration in incretin function is associated with insulin resistance, particularly type 2 diabetes. A recent study found that incretin hormone levels are lower in PCOS patients. Because of this, treating type 2 diabetes by focusing on this system has become a viable alternative, improving glycemic control and causing weight loss in affected individuals.[35]

Side effects

Although nausea and vomiting are common side effects, the primary safety concern associated with drugs acting through the GLP-1 pathway is still the potential for an increased risk of pancreatitis [42]. Two GLP-1 receptor agonists are available: ligglutide and enatide [40].

TABLE 3: Recommendations for inducing ovulation with letrozole or clomiphene [38].

	Letrozole	**Clomiphene**
Initial regimen	25 mg daily on cycle day 3-7 (5 days)	50 mg daily on cycle day 3-7 (5 days)
Indication for increase	Absence of ovulation	Absence of ovulation
How much to increase	25 mg daily increment	50 mg daily increment
Maximum daily dose	7.5 mg daily	150 mg daily
Duration of treatment	6 ovulatory cycles	6 ovulatory cycles
Confirmation of ovulation	Serum progesterone 10 nmol/L Serum progesterone > 10 nmol/L at cycle day 21-23	Serum progesterone 10 nmol/L Serum progesterone > 10 nmol/L at cycle day 21-23

SURGERY:

For PCOS women who are clomiphene-resistant or do not respond to clomiphene, laparoscopic surgery is a second-line surgical procedure for ovulation.

- **Laparoscopic Ovarian Drilling:**
  Laparoscopic Ovarian Drilling (LOD) involves repeatedly rupturing the ovary using a laser or heat source. LOD lowers the risk of multiple pregnancies and ovarian hyperstimulation [45].
- **Invitro fertilization:** When treating infertility in women with PCOS who do not have any related complications, in-vitro fertilization (IVF) is advised as a third-line course of treatment [46]

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