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UNRAVELING THE COMPLEXITIES AND IN DEPTH ANALYSIS OF POLYCYSTIC OVARY SYNDROME: A CRITICAL REVIEW

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ABSTRACT :

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting 6-20% of women of reproductive age, characterized by irregular menstrual cycles, hyperandrogenism, and infertility. PCOS can significantly impact a woman's health and quality of life. The multifaceted etiology of PCOS highlights the roles of genetic and environmental factors, insulin resistance, and hormonal imbalances. Diagnosis of PCOS is typically based on the Rotterdam criteria, which require the presence of at least two of the following three features: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries as detected by ultrasound. Management of PCOS is multidimensional and is tailored to the individual's symptoms and may include lifestyle modifications, pharmacological interventions, and, in some cases, surgical options aiming to alleviate symptoms, prevent long-term complications, and improve fertility outcomes. The present article reviews current treatment options, emphasizing lifestyle modifications and pharmacological interventions tailored to individual symptoms. Emerging treatments, such as selenium nanoparticles and novel insulin sensitizers, are explored alongside recent molecular research advancements. Insulin resistance and hyperinsulinemia are commonly associated with PCOS, exacerbating hyperandrogenism and leading to metabolic complications such as obesity, type 2 diabetes, and cardiovascular diseases. Future research should focus on elucidating the genetic basis of PCOS, optimizing therapeutic strategies, and addressing the long-term health risks associated with the condition.

HISTORY :

Polycystic ovary syndrome (PCOS) is a heterogeneous familial disorder characterized by irregular menses, clinical and/or biochemical hyperandrogenism (HA), and infertility. Depending on diagnostic criteria, the prevalence is 6–20% of reproductive-aged women. Associated comorbidities include metabolic, reproductive, and psychological conditions [1]

PCOS has also been called Stein-Leventhal syndrome. PCOS is the most common endocrine disorder in women. PCOS runs in families and affects approximately 50% of first-degree relatives. Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. PCOS is a condition that presents with ovarian dysfunction and endocrine disorders.

In 1721 Vallisneri, an Italian scientist, described a married, infertile woman with shiny ovaries with a white surface, and the size of pigeon eggs. There are suggestions that the “syndrome” was referred to as early as in the time of Hippocrates (ca. 460–377 BC). Medical notes at the time referred to women “whose menstruation is less than three days or is meagre, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant” and suggest that they may have been describing women with PCOS.All these observations fit the symptomatology of PCOS – menstrual irregularity, subfertility, masculine features and obesity. However, it was the 1934 presentation and subsequent publication by Irving Stein and Michael Leventhal that identified this condition as a reproductive disorder and proposed an effective treatment – bilateral ovarian wedge resection (BOWR) – for the associated subfertility.

The modern history of polycystic ovary syndrome (PCOS) started with the pivotal paper by Stein and Leventhal in 1935.In their paper, they commence by commenting that bilateral polycystic ovaries are usually described in association with uterine bleeding and endometrial hyperplasia. They then describe a series of patients with ovaries enlarged up to four times the normal size, associated with absent menses. They described the cortex as hypertrophied and the tunica as tough fibrotic and thickened. The cysts were follicular, contained clear fluid and were confined to the surface of the cortex, numbering from 20 to 100 in each ovary. They described the uteri as either normal sized or smaller and firmer than normal. They also reported masculinising changes in some patients, with rhomboid escutcheon and hirsutism on the arms, legs and face.

From 1935 to the end of the 1970s, the research work was focused mainly on the endocrine background of PCOS. The last two decades of the 20th century saw this focus shift to metabolic problems associated with PCOS, while in recent years we have seen advanced techniques in molecular biology derive novel insight into its underlying pathophysiology.

It was not until the early 1990s at a National Institute of Health (NIH) sponsored conference on PCOS that formal diagnostic criteria were proposed and afterwards largely utilized. Many scientists tried to explain the pathophysiology of PCOS and many studies were made. It is now accepted that it is multifactorial, partly genetic. Insulin resistance has been noted consistently among many women with PCOS, especially in those with hyperandrogenism. Using the lens of evolutionary medicine, the overlap of PCOS risk alleles in women from both European and Chinese populations suggests that PCOS is an ancient disorder. The communities of reproductive medicine and reproductive sciences have been witness to an enormous acceleration of interest in polycystic ovary syndrome (PCO) since the mid-19th century.

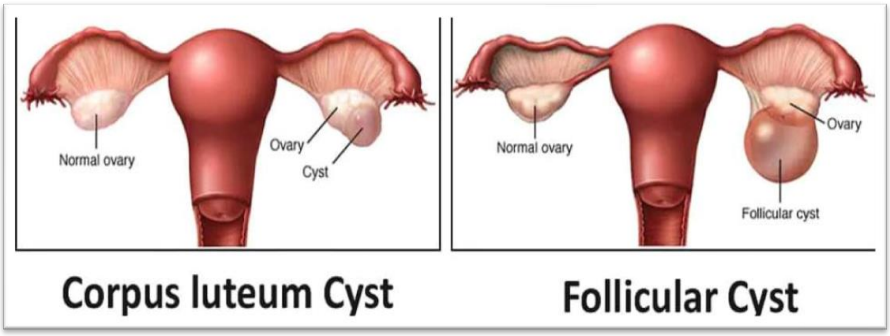


Figure 1 Type of Cysts

CAUSES AND RISK FACTORS

The cause of PCOS has not yet been definitely determined; however, it is mainly characterized by hyperandrogenism, infertility, lack of ovulation, increased level of LH, increased insulin resistance, decreased sex hormone-binding globulin (SHBG) and hirsutism.

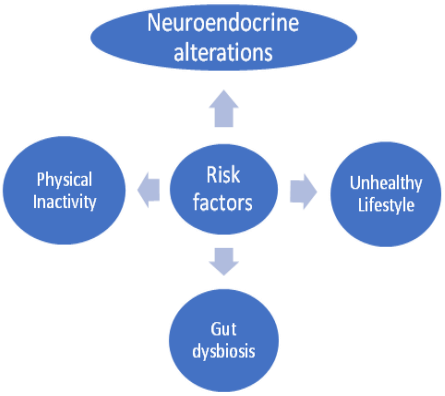
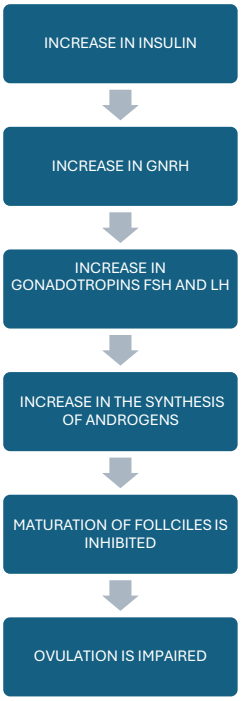


Figure 2 Risk factors of PCOD

PATHOPHYSIOLOGY

Hypothalamic neurons produce the Gonadotropin Releasing Hormone (GnRH) which is responsible for the release of Gonadotropins which include hormones like Follicle Stimulating Hormone (FSH) and LH (Luteinizing Hormone) from the Pituary Gland. In men, these hormones cause the testicles to make testosterone and in women they cause the ovaries to make estrogen and progesterone. Insulin resistance and subsequently excessive increase in insulin levels cause the frequency of GnRH to escalate, which results in increased LH/FSH. These hormone changes in the theca cells and granulosa cells (GCs) cause increase in the synthesis of androgens and decrease in the synthesis of oestradiol, and stops the maturation of follicles, leading to impaired ovulation and therefore development of PCOS.

Figure 3 Pathophysiology of PCOD



SIGN AND SYMPTOMS

PCOS is a heterogeneous condition which is defined by the presence of two out of the following criteria-
1.oligo and/or anovulation
2.hyperandrogenism
3.polycystic ovaries
The clinical manifestation of PCOS varies from a mild menstrual disorder to severe disturbance of reproductive and metabolic functions. Hyperandrogenism proceeds with symptoms like hirsutism, acne, and/or male pattern alopecia.

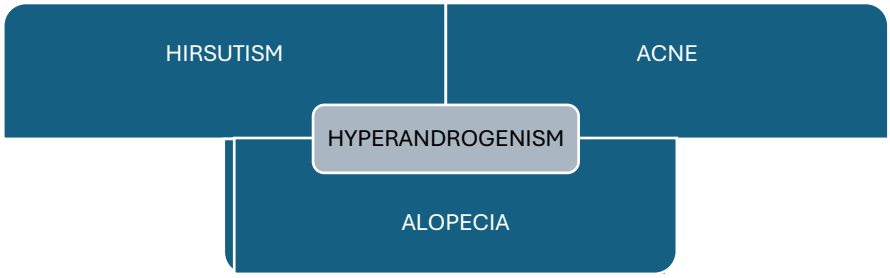


Figure 4 Symptoms associated with Hyperandrogenism

Chronic anovulation may be presented as oligomenorrhea, amenorrhea, and/or infertility.

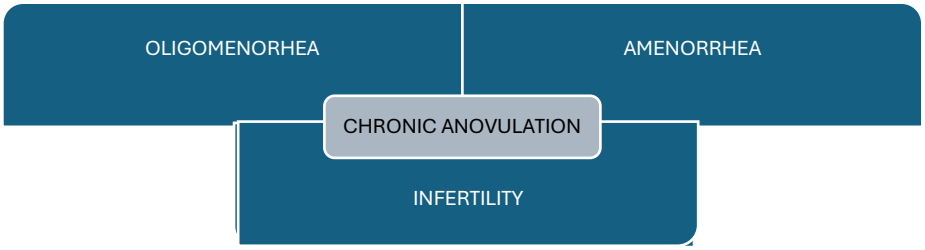


Figure 5 Symptoms associated with Chronic Anovulation

Other Clinical Manifestations include-

- Moon face
- Buffalo hump on back
- Abnormal straie
- Mood swings
- Obesity
- Insulin resistance
- Thyroid problem

Figure 6 Clinical Manifestations associated with PCOD

COMPLICATIONS

PCOS is associated with an increased risk of several comorbidities; particularly type 2 diabetes, cardiovascular disease (CVD), obesity, dyslipidaemia, hypertension and glucose intolerance.

Chronic anovulation over a long period of time is also associated with an increased risk of endometrial hyperplasia and carcinoma, which should be seriously investigated and treated.[2]

DIAGNOSIS

The diagnosing PCOS typically involves identifying at least two of the following three features:

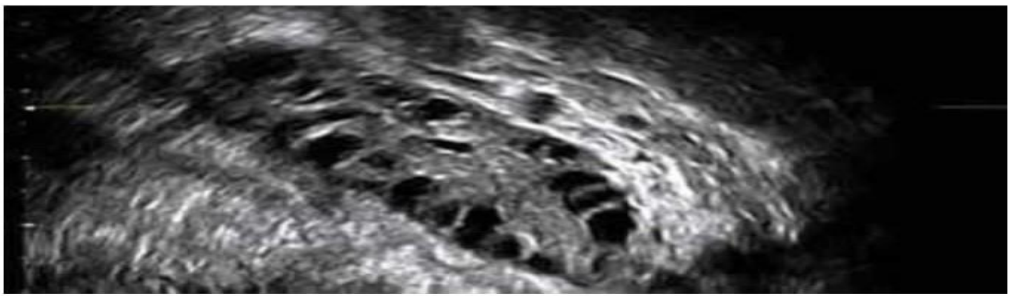
1. Irregular or absent menstrual periods.
2. Excess androgen levels, which can manifest as hirsutism, acne, or alopecia.
3. Polycystic ovaries visible on ultrasound.

Signs of hyperandrogenism (acne, hirsutism, balding(alopecia) are suggestive of the PCOS although biochemical screening helps to differentiate other causes of androgen causes. Hirsutism can be graded and given a FERRIMAN-GALLWEY SCORE by assessing the amount of hair in different parts of the body (eg -upper lip, chin, breasts, abdomen, arms and legs). It is useful to monitor the progress of hirsutism or its response to treatment by making serial records either using a chart or by taking photographs of affected areas of the body [3].

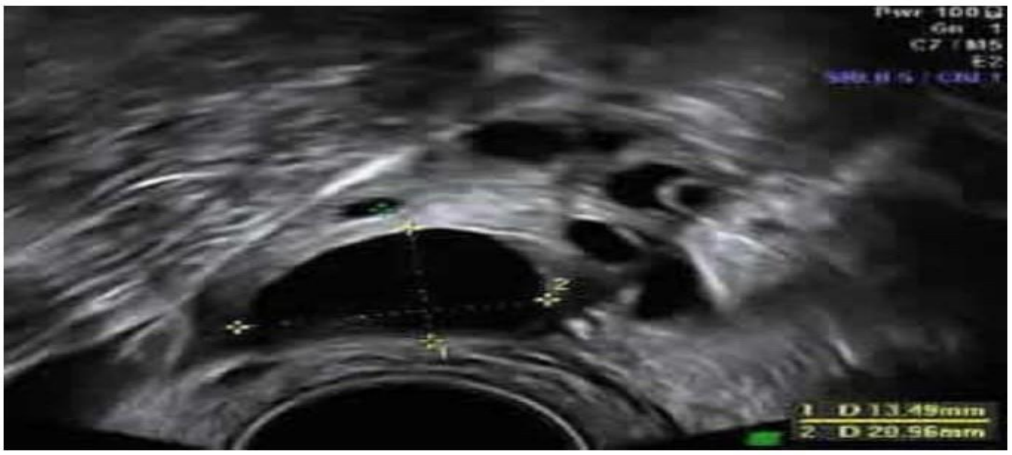
PCOS blood test Examination: They measure hormone levels, including 17-OHP, AMH, DHEA, estrogens, FSH, hCG, LH, prolactin, SHBG, testosterone, T3, T4, and TSH, when a person is diagnosed with PCOS, they also need to be tested for other conditions that are very common in people with the disease, such as diabetes and high cholesterol.

Endometrial Biopsy: An endometrial biopsy can be performed to determine if your endometrial tissue is in the correct phase or to test for endometrial cancer, which is seen more frequently in those with PCOS. This risk of endometrial cancer increases with the length of time between missed periods. During the biopsy, a small amount of tissue is removed from uterus through a thin catheter placed into through the cervix and into the uterus. This tissue is then analysed in the context of the menstrual cycle and examined for cancer cells.

Ultrasound Examination: A transvaginal ultrasound may be performed to rule out PCOS. In a transvaginal ultrasound, a probe is placed inside the vagina, which allows the healthcare provider to examine the reproductive organs and look for abnormalities. Pelvic exam or ultrasound to check ovaries to see growths in ovaries. If periods are irregular, the lining of the uterus could be thicker than normal [4]. The thickness of the endometrium can be measured. Diagnosis of "polycystic ovaries "required that at least one ovary is greater than 10 cm^3 in volume or at least one ovary has 12 or more antral follicles seen by ultrasound.



Polycystic ovary with many antral follicles



Normal ovary with a single mature follicle
Yellow cursors are measuring the follicle

Figure 7-Ultrasound report of a Normal ovary versus Polycystic ovary

CURRENT RESEARCH

We have now entered the era of molecular research of studying PCOS. Despite ongoing decades of research, it has remained a challenge to elucidate the cellular and molecular background of PCOS.

A new study has shown that extracellular vehicles (EVs) derived from mesenchymal stem cells (MSCs) can effectively treat polycystic ovary syndrome (PCOS). These EVs reduce the activity of genes responsible for high androgen production and stabilize metabolic issues in PCOS mouse models, even restoring ovarian function. This approach offers advantages over current treatments by targeting underlying causes rather than just symptoms, with potential for greater safety and lower costs. Researchers are now working towards human clinical trials and refining EV treatments to better target ovarian tissue. These EVs reduce the activity of genes responsible for high androgen production and stabilize metabolic issues in PCOS mouse models, even restoring ovarian function. This approach offers advantages over current treatments by targeting underlying causes rather than just symptoms, with potential for greater safety and lower costs. Researchers are now working towards human clinical trials and refining EV treatments to better target ovarian tissue.[5]

Bizon et al. assessed for the first time the rs2070424 polymorphism of superoxide dismutase (SOD1) in women with PCOS, detecting a dominant variant, AA (93.3%). One big outstanding piece of the PCOS pathophysiology puzzle is the metabolic question. Although metabolic parameters are not explicitly included in the current Rotterdam Criteria of PCOS, studies on the metabolic influence and implications have brought to light its critical importance [6]

Lu et al. reported that serum RANKL correlates positively with an increased risk of non-alcoholic fatty liver disease (NAFLD) in Chinese women with PCOS. This observation was found to be independent of metabolic and reproductive factors. We cannot ignore the significance and role of neuroendocrine pathophysiology in PCOS and the potential for the use of treatments which interfere with the neuroendocrine profile. Promising results have emerged in the use of new drugs—NK3R antagonists, or kappa receptor agonists. This new class of drug has been shown to decrease the activity in GnRH pulse generation (PCOS is characterized by an increase in GnRH pulse frequency) and, in turn, can decrease serum testosterone levels by up to 30%[7]

A recent study by Holzer et al. reported on their success in using letrozole for ovulation induction in women with PCOS, determining it to be independent from traditional calcium-associated signalling pathways and other parameters of calcium metabolism.[8]

TREATMENT OPTIONS

Management of women with PCOS depends on the symptoms. These could be ovulatory dysfunction-related infertility, menstrual disorders, or androgen-related symptoms.

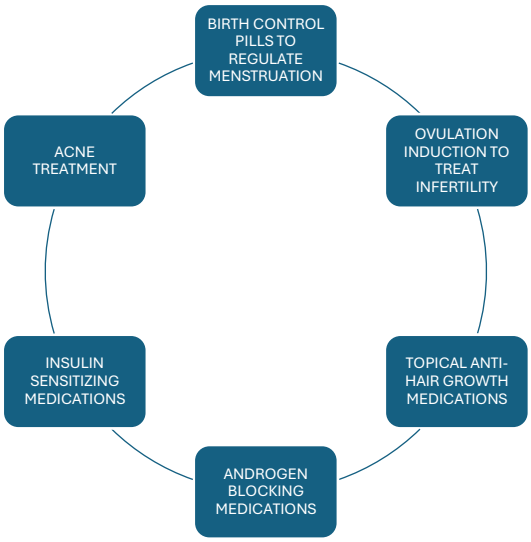


Figure 8 Treatment of PCOD

TREATMENT FOR PCOD

NON-PHARMACOLOGICAL TREATMENT

1. The clinical management of a woman with PCOS should be focused on her individual problems.
2. Obesity worsens both symptomatology and the endocrine profile and so obese women (BMI>30 kg/m2) should therefore be encouraged to lose weight. Weight loss improves the endocrine profile and increases the likelihood of ovulation and pregnancy. Normalization of menstrual cycles and ovulation could occur with modest weight loss as little as 5% of the initial weight. The treatment of obesity includes modifications in lifestyle (diet and exercise) and medical and surgical treatment. Anti-obesity drugs may help with weight loss.
3. It is sensible to keep carbohydrate content down and to avoid fatty foods.

4. Dietary advice and exercise are essential components of a weight reducing programme.

PHARMACOLOGICAL TREATMENT

Managing PCOS focuses on symptom relief and improving overall health through a combination of lifestyle changes, medication, and sometimes surgical interventions

Treatment of Menstrual Irregularity

1.Menstrual cycle control may be achieved by cyclical oral contraceptives or progestogens.

2.The easiest way is the use of a low-dose combined oral contraceptive preparation (COCP). This will result in an artificial cycle and regular shedding of the endometrium[9]

3.An alternative is a progestogen (such as medroxyprogesterone acetate or Dyhydrogesterone) for 12 days every 1-3 months to induce a withdrawal bleed.

4.Combined oral contraceptives (COCs) ; Ovocyclin-P 5 mg inj, Progynon depot 10 mg/ml inj, Bonmax, Ralotab, Esserm 60 mg tab are commonly used to regulate menstrual cycles[10]

THERAPEUTIC USES OF DRUGS USED IN PCOD

ANTI ANDROGENS

Medicines called anti-androgens may reduce hair growth and clear acne are often combined with birth control pills. Anti-androgens like spironolactone, Cyproterone acetate flutamide, and finasteride help manage hyperandrogenism by reducing androgen levels in the body[11] These medications are particularly useful for treating polycystic ovary syndrome (PCOS) because they help reduce symptoms such as excessive hair growth (hirsutism) and other issues related to high androgen levels. Although each of these medications works slightly differently, they all block the action of testosterone.

INSULIN SENSITIZERS:

In PCOS condition, Insulin doesn't work properly. This poor insulin function leads to higher insulin levels in the body, which can cause the ovaries to produce more androgens (male hormones). These higher androgen levels can stop the normal development of eggs in the ovaries, leading to PCOS symptoms like irregular periods and ovarian cysts. Insulin resistance not only causes PCOS symptoms but also increases the risk of developing long-term health issues like type 2 diabetes and heart disease. Medications called insulin sensitizers, such as metformin and thiazolidinediones (TZDs), help the body use insulin better.[11-12] Metformin helps by reducing the amount of glucose produced by the liver and increasing the uptake of glucose by cells. This improves ovulation, reduces male hormone levels, and makes menstrual cycles more regular. Metformin can also help with weight loss and improve cholesterol levels. Thiazolidinediones, like pioglitazone, also improve insulin sensitivity and help lower male hormone levels, which can improve ovulation and menstrual cycles. Research shows that using both metformin and TZDs together is often more effective than using metformin alone in managing PCOS symptoms and improving insulin resistance [13]. So, by using these medications and making lifestyle changes like diet and exercise, women with PCOS can better manage their symptoms and reduce the risk of long-term health problems.

Ovulation Induction drugs like Clomiphene Citrate is often the first-line treatment for inducing ovulation in women with PCOS who wish to conceive. Letrozole is also used for ovulation induction, especially for those who do not respond to clomiphene citrate. [14]

Laparoscopic Ovarian Drilling for women who do not respond to medication for ovulation induction. It involves creating small holes in the ovaries to reduce androgen production and stimulate ovulation.

Figure 9 Ovarian drilling

CONVENTIONAL MARKET FORMULATION

TABLE 1-CONVENTIONAL FORMULATIONS OF DRUGS USED IN PCOD

Type	Content	Brand name	Company name	Dose	Price
Oral tablet	Metformin	Glycomet	USV Pvt Ltd	500mg, 800mg, 1000mg	Rs. 50 -100 for 10 tablets
Oral tablet	Clomiphene	Fertyl	Torrent Pharma	50mg	Rs. 75- 100 for 5 tablets
Oral tablet	Letrozole	Letroz	Cipla	2.5mg	Rs. 100-150 for 5 tablets
Oral tablet	Ethinyl Estradiol + Cyproterone Acetate	Krimson 35	Zydus Cadila	2mg +0.035 mg	Rs. 300-400 for 21 tablets
Oral tablet	Spironolactone	Aldactone	PRG Life Sciences	25mg, 50mg,100mg	Rs. 40-7- for 10 tablets
Oral tablet	Pioglitazone	Pioz	USV Pvt Ltd	15mg,30mg	Rs 30-50 for 10 tablets
Oral Tablet	Letrozole for Ovulation induction	Letrozole	Cipla	2.5mg	Rs 100-150 for 5 tablets
Oral Powder	Myo-Inositol + D-chiro Inositol	Ova care Myo	Meyer organics	1 sachet daily	Rs. 700-900 for 30 sachets
Injection	Gonadotrophins (FSH)	Gonal-f	Merck Serono	75IU, 150IU, 450IU	Rs. 4500-6000 per injection
Topical cream	Eflornithine	Eflora	Ranbaxy	13.9% cream	Rs. 1200 – 1500 per 15g tube

NOVEL FORMULATED DRUG FORMULATIONS

Selenium nanoparticles (Se-NPs) have emerged as a promising treatment for polycystic ovary syndrome (PCOS), particularly in managing hyperlipidaemia, antiandrogenic hyperinsulinemia, and oxidative stress. Studies have shown that Se-NPs exhibit higher antioxidant activity compared to selenium (Se) alone, making them a superior choice in combating oxidative stress associated with PCOS[15]

Novel therapeutic modalities for treatment/management of PCOS, like use of newer insulin sensitizers viz., Inositols, Glucagon-like peptide-1(GLP-1) agonists, Dipeptidyl pepdidase-4 (DPP-4) inhibitors, and sodium-glucose transport protein 2 (SGLT2) inhibitors are currently being considered[16]

TABLE 2:NOVEL FORMULATIONS OF DRUGS USED IN PCOD

Type	Content	Brand name	Company name	Dose	Price (INR)
Sustained Release tablets	Myo-inositol, D-chiro-inositol	Oosure – M	La Renon Healthcare	1 tablet daily	Rs. 500 for 10 tablets
Controlled Release	Myo-inositol, D-chiro-inositol	Folinz	Lupi Pharma	1 sachet daily	Rs. 600 for 30 sachets
Extended Release	Myo-inositol, D-chiro-inositol	Fertisure –F	Sun pharmaceuticals	1 sachet daily	Rs 720 for 30 sachets

Sustained Release tablets	Myo-inositol, D-chiro-inositol, l-methyl folate, vit D3	Ovabless	Alniche life sciences	1 tablet daily	Rs. 800 for 30 tablets
Controlled Release	Myo-inositol, D-chiro-inositol, l-methyl folate, vit D3	Ovaflow	Shild Healthcare	1 sachet daily	Rs 750 for 30 sachets

CONCLUSION :

Polycystic Ovary Syndrome (PCOS) is a complex and multifaceted health condition that affects millions of women worldwide which is characterized by hormonal imbalances, irregular menstrual cycles, and the presence of ovarian cysts, PCOS can significantly impact a woman's quality of life. Despite its prevalence, the exact cause of PCOS remains unclear, although factors such as genetics, insulin resistance, and lifestyle play substantial roles. Effective management of PCOS requires a holistic approach that includes lifestyle modifications, medical treatments, and regular monitoring. Lifestyle changes, particularly those involving a healthy balanced diet and exercise, have been shown to improve symptoms and reduce the risk of long-term complications like type 2 diabetes and cardiovascular disease. Medications can help regulate menstrual cycles, manage symptoms, and address fertility issues. Ongoing research continues to enhance our understanding of PCOS and improve treatment options. Increased awareness and education about PCOS are crucial for early diagnosis and intervention, which can mitigate the condition's adverse effects on health and well-being. While PCOS presents significant reproductive and metabolic challenges, comprehensive management strategies and ongoing continued research offer hope for better outcomes. By fostering a supportive environment and empowering women with knowledge, we can improve the lives of those affected by this condition.

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