From Pathophysiology to Treatment: Navigating the Challenges of Polycystic Ovary Syndrome

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Abstract: Polycystic Ovary Syndrome (PCOS) is a common but complex endocrine disorder that affects a significant number of women of reproductive age. It is characterized by a range of symptoms, including irregular menstrual cycles, hyperandrogenism (excessive male hormones leading to symptoms such as hirsutism and acne), and the presence of multiple cysts in the ovaries. However, PCOS is not limited to reproductive health; it has profound metabolic implications, increasing the risk of obesity, insulin resistance, Type 2 Diabetes Mellitus, and cardiovascular diseases. The pathophysiology of PCOS remains incompletely understood, but it is thought to involve hormonal imbalances, including elevated levels of luteinizing hormone (LH) and insulin resistance, which contribute to ovarian dysfunction and anovulation. The disorder's molecular mechanisms are still being studied, with genetic and environmental factors likely playing roles in its development. One of the challenges in diagnosing PCOS is its heterogeneity, as the severity and presence of symptoms can vary greatly between individuals. This has led to multiple diagnostic criteria, with the Rotterdam Criteria being the most widely accepted, requiring at least two of the following three features: irregular ovulation, hyperandrogenism, and polycystic ovaries. Treatment for PCOS typically includes both pharmacological and non-pharmacological strategies. Pharmacologically, oral contraceptives are commonly used to regulate menstrual cycles and reduce hyperandrogenism, while medications like metformin can help address insulin resistance. Non-pharmacological approaches, such as weight management and lifestyle modifications, are also important in improving metabolic health. New avenues for research are focusing on the molecular pathways involved in PCOS, with an emphasis on developing personalized therapies that target the underlying causes of the disorder rather than just alleviating symptoms.

Keywords: Polycystic Ovary Syndrome, Irregular Menstrual Cycles, Hyperandrogenism, Insulin Resistance, Ovulation, Metabolic Implications.

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age, with an estimated 6-12% of women worldwide impacted by the condition. PCOS is associated with a broad spectrum of clinical manifestations that affect various aspects of a woman's health, including reproductive, metabolic, and psychological well-being. The disorder is complex and multifactorial, with genetic, hormonal, and environmental factors all contributing to its development. Despite its high prevalence, the exact cause of PCOS remains elusive, but ongoing research continues

to shed light on its underlying mechanisms. Early diagnosis and effective management are critical in alleviating symptoms and preventing long-term complications such as infertility, diabetes, and cardiovascular diseases. One of the most common features of PCOS is menstrual irregularity, which affects the vast majority of women with the condition [1]. Most women with PCOS experience infrequent, absent, or irregular periods due to anovulation, a key characteristic of the disorder. Anovulation occurs when the ovaries do not release eggs regularly, disrupting the menstrual cycle. This irregularity in the menstrual cycle is often the first symptom that prompts women to seek medical attention. The absence of regular ovulation can also lead to significant reproductive challenges, including infertility. Due to anovulation, women with PCOS may struggle to conceive, and PCOS is one of the leading causes of infertility in women [2]. However, many women with the disorder are able to conceive with the help of fertility treatments such as ovulation-inducing drugs or assisted reproductive technologies like in vitro fertilization (IVF). Another key feature of PCOS is hyperandrogenism, which is characterized by an excess of male hormones, particularly testosterone. This hormonal imbalance leads to several physical symptoms, including hirsutism (excessive hair growth, particularly on the face, chest, and abdomen), acne, and alopecia (thinning or loss of hair on the scalp). These symptoms are often distressing and can have a significant psychological impact, leading to issues related to self-esteem and quality of life. While the severity of hyperandrogenism varies among women with PCOS, it remains a hallmark symptom of the disorder that requires effective management to improve both physical appearance and emotional well-being [3].

Beyond the reproductive and cosmetic symptoms, PCOS is also associated with significant metabolic disturbances. Obesity is prevalent in many women with PCOS, and it often worsens other metabolic issues associated with the condition. Women with PCOS are more likely to be overweight or obese, and the excess body weight can exacerbate insulin resistance, one of the underlying mechanisms of the disorder. Insulin resistance occurs when the body's cells become less responsive to insulin, a hormone that regulates blood sugar. As a result, the pancreas compensates by producing more insulin. The elevated levels of insulin in the bloodstream (known as hyperinsulinemia) contribute to weight gain, further aggravating the metabolic complications of PCOS. Insulin resistance is also closely linked to the development of Type 2 diabetes, making it a major concern for women with the condition [4]. Furthermore, insulin resistance can lead to dyslipidemia, which is the abnormal regulation of cholesterol and other lipids in the blood, increasing the risk of cardiovascular diseases such as heart disease and stroke. Women with PCOS have a higher risk of developing metabolic syndrome, a cluster of conditions including high blood pressure, high blood sugar, abnormal cholesterol levels, and excess body fat around the waist, which together increase the risk of cardiovascular disease. The pathophysiology of PCOS remains complex and not fully understood, though research suggests that genetic factors play a significant role in its development. Women with a family history of PCOS are more likely to develop the condition themselves, suggesting a hereditary component. In addition to genetic factors, hormonal imbalances are central to the development of PCOS. High levels of luteinizing hormone (LH) and insulin are common in women with PCOS, leading to ovarian dysfunction and the characteristic cysts that appear on the ovaries. Elevated insulin levels contribute to increased androgen production in the ovaries, which in turn leads to hyperandrogenism. The interplay between genetics, hormonal factors, and environmental influences such as diet, lifestyle, and stress can contribute to the development and severity of PCOS [5].

Diagnosing PCOS can be challenging due to the **heterogeneity** of symptoms. While some women experience more pronounced symptoms such as severe hirsutism and obesity, others may have only mild manifestations or none at all. There are several diagnostic criteria for PCOS, with the **Rotterdam Criteria** being the most widely accepted. According to these criteria, a diagnosis of PCOS can be made if a woman exhibits at least two of the following three features: irregular ovulation (manifested as irregular or absent periods), clinical or biochemical evidence of hyperandrogenism, and polycystic ovaries observed via ultrasound. Given the wide range of symptoms and potential health risks associated with PCOS, early diagnosis and **effective management** are essential. Treatment strategies aim to address the specific symptoms experienced by the patient, with a combination of

pharmacological and **non-pharmacological** approaches. Oral contraceptives are often used to regulate menstrual cycles and reduce androgen levels, while medications like metformin are prescribed to manage insulin resistance. **Lifestyle changes**, including weight management, regular physical activity, and a balanced diet, are essential for improving metabolic health and reducing the risk of Type 2 diabetes and cardiovascular disease [6].

Pathophysiology of PCOS

The pathophysiology of Polycystic Ovary Syndrome (PCOS) is multifactorial, involving an imbalance in ovarian steroidogenesis, insulin resistance, and dysfunction of the hypothalamic-pituitary-ovarian (HPO) axis. Central to the disorder is the increased secretion of luteinizing hormone (LH), which disrupts the delicate balance between LH and follicle-stimulating hormone (FSH). This hormonal imbalance leads to **anovulation**, where the ovaries fail to release eggs regularly, a hallmark of PCOS. The disturbance in follicular development results in the formation of cystic follicles in the ovaries, a characteristic feature visible on ultrasound. Elevated levels of androgens, particularly testosterone, are another key aspect of PCOS pathophysiology. These elevated androgen levels contribute to many of the clinical symptoms of PCOS, including **hirsutism** (excessive hair growth on the face and body), acne, and alopecia (thinning or loss of scalp hair). These symptoms arise because androgens promote the growth of excess hair and alter the skin's sebaceous glands, leading to acne. The higher levels of testosterone are thought to result from the increased secretion of LH, which stimulates the ovaries and adrenal glands to produce androgens [7]. Another significant contributor to PCOS is insulin resistance, which occurs when the body's cells become less responsive to insulin. In response, the pancreas produces more insulin, leading to hyperinsulinemia. Elevated insulin levels, in turn, exacerbate hyperandrogenism by stimulating the ovaries and adrenal glands to produce even more testosterone. Insulin resistance also increases the risk of developing **obesity**, which is commonly seen in women with PCOS. Obesity further worsens insulin resistance and amplifies the severity of symptoms, creating a vicious cycle that complicates both the clinical management of PCOS and its associated metabolic disturbances, such as Type 2 diabetes and cardiovascular disease. These interconnected pathophysiological mechanisms contribute to the complexity of PCOS, underscoring the need for a comprehensive and individualized approach to its diagnosis and management [8].

Diagnostic Criteria

The diagnosis of Polycystic Ovary Syndrome (PCOS) is based on a combination of clinical, biochemical, and ultrasonographic criteria. Among the various diagnostic approaches, the most widely accepted are the **Rotterdam criteria**, which require the presence of at least two of the following three features: irregular ovulation, hyperandrogenism, and polycystic ovaries. Irregular ovulation is commonly observed in women with PCOS, often manifesting as oligomenorrhea (infrequent periods) or amenorrhea (absence of periods). These menstrual irregularities arise due to anovulation, where the ovaries fail to release eggs regularly. Anovulation is a hallmark of PCOS and is the main reason many women with the condition experience difficulty in conceiving. Hyperandrogenism is another key feature of PCOS, characterized by elevated levels of male hormones such as testosterone. This hormonal imbalance can manifest in clinical symptoms such as hirsutism (excessive hair growth on the face, chest, and abdomen), acne, and alopecia (thinning or loss of hair on the scalp). Biochemical signs, such as elevated testosterone levels in blood tests, are also indicative of hyperandrogenism. These symptoms contribute to the significant cosmetic and psychological burden faced by many women with PCOS [9-10]. Polycystic ovaries are another critical criterion for diagnosis. These ovaries can be identified on ultrasound, where they typically appear as having 12 or more small follicles (measuring 2-9 mm in diameter) in each ovary. These cysts represent arrested follicles that failed to mature, a result of the hormonal imbalance in PCOS. One of the primary challenges in diagnosing PCOS is its heterogeneity. Not all women with PCOS exhibit the same combination of symptoms, and some may have subtle or minimal clinical manifestations. This variability can make diagnosis more difficult, as some women may not present with obvious symptoms such as hirsutism or irregular cycles. Moreover, other conditions like thyroid dysfunction, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia can mimic the symptoms of PCOS, further complicating the

diagnostic process. Therefore, it is essential to conduct a comprehensive evaluation, including clinical assessment, laboratory tests, and ultrasound, to accurately diagnose PCOS and differentiate it from other conditions with overlapping symptoms. Early and accurate diagnosis is crucial for the proper management of PCOS, as it allows for timely intervention and can help prevent the long-term complications associated with the condition, such as infertility, metabolic syndrome, and cardiovascular diseases [11].

Challenges in Managing PCOS

The management of **Polycystic Ovary Syndrome** (**PCOS**) is multifaceted and requires an individualized approach due to the wide variety of symptoms and potential long-term health risks associated with the disorder. Since PCOS can present with different combinations of **reproductive**, **metabolic**, and **cosmetic** issues, it is essential that treatment plans be tailored to the specific needs of each patient. The goal of treatment is to alleviate symptoms, improve overall health, and reduce the risk of long-term complications, such as infertility, Type 2 diabetes, and cardiovascular diseases. For patients presenting with **irregular menstrual cycles** and **anovulation**, the first line of treatment often involves **oral contraceptives**. These help regulate menstrual cycles and manage **hyperandrogenism** (excessive male hormones), which can lead to symptoms like **hirsutism**, **acne**, and **alopecia**. Oral contraceptives suppress the production of **luteinizing hormone** (**LH**) and reduce androgen levels, effectively improving many of the symptoms associated with PCOS. For women seeking pregnancy, **fertility treatments** such as **clomiphene citrate** or **letrozole** may be used to induce ovulation and improve the chances of conception [11-12].

Metformin, an insulin-sensitizing agent, is frequently prescribed for women with insulin resistance or **obesity**. It helps lower blood sugar levels and may improve **ovarian function** in some women with PCOS. Metformin is particularly beneficial for those at high risk for Type 2 diabetes and can also support weight management. However, weight loss alone, through lifestyle changes like dietary modifications and regular physical activity, is often one of the most effective interventions. Even modest weight loss (5-10% of total body weight) can significantly improve insulin sensitivity, reduce androgen levels, and restore regular menstrual cycles. For women with more severe **hirsutism** or **acne**, anti-androgen medications such as spironolactone may be prescribed to block the effects of excess testosterone [13]. These medications are typically used in conjunction with oral contraceptives for more comprehensive symptom management. In addition to pharmacological treatment, lifestyle modifications, including weight management, dietary changes, and exercise, are crucial for managing the metabolic disturbances commonly seen in PCOS. Regular physical activity can improve insulin sensitivity, reduce weight, and lower the risk of developing Type 2 diabetes and cardiovascular disease. Because PCOS is a complex and variable disorder, ongoing monitoring and individualized treatment plans are essential to address each patient's unique symptoms and health risks. By focusing on both short-term symptom relief and long-term health outcomes, healthcare providers can help women with PCOS lead healthier, more balanced lives [14-15].

Reproductive Management

Infertility is one of the most distressing symptoms for women with Polycystic Ovary Syndrome (PCOS), as **anovulation** (lack of ovulation) is a primary cause of difficulty conceiving. Anovulation leads to irregular or absent menstrual cycles, which in turn affects the ability to release eggs for fertilization. For women with PCOS who wish to conceive, **ovulation induction** is a common and effective treatment approach. This typically involves medications such as **clomiphene citrate**, **letrozole**, or **gonadotropins**, which stimulate the ovaries to produce and release eggs. Clomiphene citrate and letrozole are usually first-line treatments due to their ability to induce ovulation with relatively low risks. Gonadotropins, which are injectable hormones, may be used in cases where oral medications are ineffective, although they come with a higher risk of multiple pregnancies. In cases where **ovulation induction** treatments are unsuccessful or if the patient is dealing with more severe infertility issues, **in vitro fertilization (IVF)** may be considered. IVF is a more advanced fertility treatment in which eggs are retrieved from the ovaries, fertilized in a lab, and then implanted into the

uterus. IVF is often recommended when other fertility treatments have not led to successful pregnancy outcomes [15-17]. In addition to fertility treatments, women with PCOS often require **oral contraceptives (OCs)** or **progestins** to manage symptoms and regulate their menstrual cycles. Oral contraceptives are commonly prescribed to regulate the menstrual cycle, reduce the risk of **endometrial hyperplasia** (thickening of the uterine lining), and manage symptoms of **hyperandrogenism**, such as **hirsutism** (excessive hair growth), **acne**, and **alopecia**. Progestins may also be used to help regulate bleeding and prevent endometrial buildup, ensuring overall reproductive health [17-20].

Management of Hyperandrogenism

Hyperandrogenism is a hallmark feature of Polycystic Ovary Syndrome (PCOS) and manifests in symptoms such as **hirsutism** (excessive hair growth), **acne**, and **male-pattern baldness**. These symptoms are primarily caused by elevated levels of male hormones (androgens), particularly testosterone, which disrupt normal female hormone balance. The first-line treatment for **hirsutism** and **acne** in women with PCOS typically includes **oral contraceptives (OCs)**. OCs work by suppressing ovarian androgen production, reducing the levels of circulating testosterone. This helps alleviate symptoms like hirsutism and acne while also regulating menstrual cycles. Additionally, **anti-androgenic agents**, such as **spironolactone**, may be used to directly block the effects of androgens on hair follicles and sebaceous glands, further helping to reduce symptoms of hyperandrogenism. For more severe cases of **hirsutism**, where medication alone may not be sufficient, **laser hair removal** or **electrolysis** can be considered as cosmetic treatments. These methods target hair follicles, offering long-term or permanent hair reduction. While these treatments help manage the symptoms of hyperandrogenism in PCOS, a comprehensive approach, including medications and lifestyle interventions, is often necessary to address the condition's full spectrum of effects [20-22].

Metabolic Management

The metabolic implications of Polycystic Ovary Syndrome (PCOS) are profound, as many women with the condition experience insulin resistance, which significantly impacts their overall health and increases their risk for developing a range of long-term complications, including Type 2 diabetes, hypertension, and cardiovascular diseases. Insulin resistance occurs when the body's cells become less responsive to insulin, requiring the pancreas to produce more insulin to maintain normal blood glucose levels. Over time, this leads to hyperinsulinemia (elevated insulin levels), which further exacerbates the metabolic abnormalities seen in PCOS. These metabolic issues, along with **obesity** (which is commonly associated with PCOS), create a vicious cycle that can worsen insulin resistance, elevate androgen levels, and contribute to the development of diabetes and heart disease. The management of metabolic concerns in PCOS is crucial to prevent these long-term complications [23]. The cornerstone of metabolic management is lifestyle modification, which includes dietary changes and increased physical activity. Weight loss, even modest (around 5-10% of total body weight), has been shown to improve insulin sensitivity, reduce androgen levels, and restore ovarian function, leading to more regular menstrual cycles and improved fertility. Dietary changes that focus on low glycemic index foods, increased fiber, and healthy fats, as well as regular exercise, can help control blood sugar levels and reduce body fat. These lifestyle modifications are essential not only for improving insulin resistance but also for managing symptoms such as hirsutism, acne, and ovulatory dysfunction, which are common in PCOS. In addition to lifestyle changes, pharmacological options play a vital role in addressing insulin resistance and other metabolic abnormalities in women with PCOS. The most commonly prescribed medication is **metformin**, which works by improving **insulin** sensitivity. Metformin has been shown to help reduce blood glucose levels, lower insulin resistance, and even promote ovulation in women with PCOS, making it a valuable tool for both metabolic management and fertility enhancement. In some cases, metformin can also regulate menstrual cycles and improve lipid profiles by reducing triglycerides and cholesterol levels [24-25].

Other pharmacological agents are being explored for their potential benefits in managing the metabolic aspects of PCOS. One such class of medications is **thiazolidinediones** (**TZDs**), such as **pioglitazone**.

TZDs improve insulin sensitivity by enhancing the effectiveness of insulin in peripheral tissues, including muscle and fat. While promising, the use of TZDs in PCOS requires careful consideration of potential side effects, including weight gain and increased risk of edema, which can complicate management in certain patients. Another class of drugs that is being studied for its metabolic benefits in PCOS are **GLP-1 receptor agonists** (e.g., **liraglutide**). These medications, which are commonly used in the management of **Type 2 diabetes**, work by increasing insulin secretion in response to meals, decreasing glucagon secretion (which helps to reduce blood sugar levels), and slowing gastric emptying, which helps with weight loss. Research suggests that **GLP-1 receptor agonists** may help improve **insulin sensitivity** and promote **weight loss**, both of which are beneficial for women with PCOS. Additionally, these medications may reduce the risk of cardiovascular diseases, making them an attractive option for patients with PCOS who are at higher risk for heart disease due to insulin resistance [26-30].

The management of **metabolic abnormalities** in PCOS requires a multi-faceted approach, combining lifestyle modifications with pharmacological treatments. While **insulin resistance** is a core feature of PCOS, addressing other aspects of the condition, such as **hyperandrogenism**, **obesity**, and **dyslipidemia**, is equally important in reducing the risk of long-term complications. Early intervention with lifestyle changes, medications like **metformin**, and emerging treatments like **GLP-1 receptor agonists** may help to improve insulin sensitivity, reduce metabolic risks, and prevent the development of **Type 2 diabetes**, **hypertension**, and **cardiovascular diseases** in women with PCOS. Overall, managing the metabolic aspect of PCOS is crucial not only for improving fertility and reproductive health but also for minimizing the long-term risks associated with the disorder. As research into PCOS continues, new therapeutic options will likely emerge, offering further promise for improving the quality of life and health outcomes for women living with this complex condition [3].

New Directions in Treatment

Recent research has led to new insights into the molecular mechanisms of **Polycystic Ovary Syndrome (PCOS)**, advancing our understanding of the condition and driving the development of novel therapeutic approaches. PCOS, a complex endocrine disorder, has long been associated with **insulin resistance, hyperandrogenism**, and **ovarian dysfunction**. However, new studies have begun to uncover the intricate molecular pathways involved in these processes, offering hope for more targeted and effective treatments in the future. One promising area of research involves **targeting the insulin signaling pathway**. As insulin resistance is a key feature of PCOS, disrupting normal insulin signaling can contribute to several of the metabolic and reproductive disturbances seen in affected women. Advances in understanding how insulin interacts with key signaling molecules in various tissues, including the ovaries, muscle, and liver, are leading to the development of drugs that can better manage insulin sensitivity. Researchers are investigating **insulin sensitizers** beyond traditional agents like **metformin**, exploring new pharmacological options that can restore normal insulin function more effectively, improving both metabolic and reproductive health [30-32].

In addition to insulin signaling, **anti-inflammatory agents** are emerging as a potential therapeutic strategy for PCOS. Recent studies have highlighted the role of **chronic low-grade inflammation** in the pathophysiology of PCOS, with inflammation being implicated in insulin resistance and **hyperandrogenism**. Women with PCOS often exhibit elevated levels of inflammatory markers, such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF- α). This chronic inflammation contributes to the development of insulin resistance and may also exacerbate the androgenic symptoms of PCOS, such as **hirsutism** and **acne**. As a result, researchers are exploring anti-inflammatory medications and lifestyle interventions that may reduce inflammation and improve both metabolic and reproductive outcomes in women with PCOS. **Genetic and epigenetic factors** are also being increasingly recognized as key contributors to the development of PCOS [33-35]. Advances in genomics have revealed that genetic predisposition plays a significant role in determining susceptibility to the condition, with several candidate genes linked to ovarian function, insulin signaling, and hormonal regulation. Additionally, **epigenetic modifications**—changes in gene expression that do not involve alterations to the underlying DNA sequence—are also believed to

influence the development of PCOS. Environmental factors, such as diet, stress, and exposure to endocrine-disrupting chemicals, can potentially alter gene expression patterns and exacerbate the symptoms of PCOS. As research continues, understanding the epigenetic mechanisms behind PCOS may offer new opportunities for **precision medicine**, enabling more personalized treatment strategies based on individual genetic and environmental factors. Despite the promising progress in molecular research, lifestyle interventions remain a cornerstone of managing PCOS. Recent studies have provided further evidence supporting the effectiveness of low-carbohydrate diets in improving both metabolic and reproductive outcomes in women with PCOS [35-37]. Diets that reduce carbohydrate intake have been shown to improve insulin sensitivity, promote weight loss, and regulate menstrual cycles. Low-carb diets may also reduce androgen levels, thereby alleviating symptoms like **hirsutism** and acne. While a variety of dietary approaches can be effective, emphasizing whole foods, lean proteins, and healthy fats is key for optimizing metabolic health in women with PCOS. Moreover, mindfulness-based interventions, including stress management techniques such as yoga, meditation, and mindful eating, are gaining attention for their potential benefits in PCOS management. Chronic stress is known to exacerbate insulin resistance and hormonal imbalances, and mindfulness-based practices may help reduce cortisol levels, improve emotional well-being, and potentially improve metabolic function. Emerging evidence suggests that incorporating mindfulness practices into daily routines can improve both psychological and physiological outcomes, making them a valuable addition to conventional treatment regimens [37-40].

Conclusion

Polycystic Ovary Syndrome (PCOS) remains a complex and multifactorial condition that affects women of reproductive age, with significant reproductive and metabolic implications. The condition is characterized by irregular ovulation, hyperandrogenism, and the presence of polycystic ovaries, leading to symptoms such as infertility, hirsutism, acne, and obesity. Furthermore, women with PCOS are at an increased risk for developing insulin resistance, Type 2 diabetes, and cardiovascular diseases. Given the wide range of symptoms and potential long-term health risks, early diagnosis and a tailored, multifaceted approach to treatment are essential for managing the condition effectively. The management of PCOS requires addressing both reproductive and metabolic concerns. Pharmacological treatments like oral contraceptives and anti-androgens are commonly used to regulate menstrual cycles and manage symptoms of hyperandrogenism. Metformin, an insulinsensitizing agent, is frequently prescribed to improve insulin resistance and regulate glucose levels. Lifestyle modifications, including dietary changes and regular physical activity, are crucial for improving insulin sensitivity and managing weight. Despite the challenges in managing PCOS, recent advances in understanding the **pathophysiology** of the condition offer hope for improved therapies. Research focusing on the molecular and genetic underpinnings of PCOS is expanding, with a particular focus on the role of insulin resistance, androgen excess, and the hypothalamic-pituitaryovarian axis. These insights are likely to lead to more personalized treatment strategies, improving reproductive outcomes and reducing long-term health risks. With ongoing research, future therapies may provide more effective, individualized treatments, ultimately enhancing the quality of life for women with PCOS.

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