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A brief report on PCOS: and its inducing model

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ABSTRACT: -
The pathogenesis of polycystic ovarian syndrome (PCOS), a prevalent endocrine condition among women of reproductive age and a primary cause of infertility, is not entirely understood. Nine to eight percent of women in their reproductive years suffer from polycystic ovarian syndrome (PCOS), which results in hyperandrogenism and infertility because of abnormal follicular maturation and anovulation.
Information from experimental animal models may contribute to a better understanding of the mechanisms behind the onset and progression of PCOS, as the etiology of the condition is still poorly understood. Women's ovaries, which are reproductive organs that produce progesterone and estrogen hormones that aid in controlling the menstrual cycle, as well as trace amounts of relaxin, inhibin, and male hormones known as androgens, are affected by PCOD, also known as PCOS. A disorder known as PCOD (Polycystic Ovarian Disease) occurs when a woman's ovaries generate a lot of immature or partially mature eggs, which eventually develop into ovarian cysts. This results in enlarged ovaries that release a lot of androgens, or male hormones, which lead to abnormal weight gain, irregular menstruation cycles, hair loss, and infertility. The two most commonly utilized inducing models are dehydroepiandrosterone (DHEA) and 5α-dihydrotestosterone (DHT).

KEYWORDS: -polycystic ovary syndrome, androgen, animal inducing models

I. INTRODUCTION: -

Women's ovaries, which are reproductive organs that produce progesterone and estrogen hormones that aid in controlling the menstrual cycle, as well as trace amounts of relaxin, inhibin, and male hormones known as androgens, are affected by PCOD, also known as PCOS. The appearance of ovarian cysts, anovulation, and endocrine variation are the hallmarks of PCOS, a diverse endocrine illness that significantly affects a woman's life.[1] In addition to affecting reproductive function, this diverse disease is linked to the development of type 2 diabetes, cardiovascular disease, and endometrial cancer. Patients frequently have metabolic abnormalities such as insulin resistance, metabolic syndrome, and obesity.[2]

Polycystic ovaries, oligo/anovulation, and clinical or biochemical hyperandrogenism are the three characteristics that define PCOS. Clinically, these symptoms are linked to hyperandrogenism, which results in hirsutism and acne, and decreased fertility, which is caused by defective follicular maturation and the ensuing anovulation. In women with PCOS, increased ovarian volume and abnormal folliculogenesis—which is manifested by numerous cystic follicles between 2 and 9 mm—are associated with both chronic anovulation and androgen excess.[3]

In young women of reproductive age, PCOS can present clinically as oligo-ovulation, biochemical or clinical hyperandrogenism, hirsutism, male pattern baldness, acne, acanthosis nigricans, and polycystic ovaries. It also has a lengthy prodrome with detectable abnormalities that manifest as the metabolic syndrome, such as obesity, hypertension, atherosclerosis, elevated cardiovascular risk, PCOS, and dyslipidemia due to a decrease in HDL cholesterol and hypertriglyceridemia. Many animal models have been used to study the causes of PCOS and how to treat it. By choosing the right animal model, each of these characteristics can be examined separately.[4]

Parallel to this, PCOS patients also have lower levels of HDL and increased levels of triglycerides, total cholesterol, and low-density lipoprotein (LDL). The balance of sex hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone, and testosterone, is disrupted in women with

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PCOS. Insulin insensitivity also results in higher blood glucose levels.Evidence indicated that an increase in the frequency and amplitude of the hypothalamic GnRH pulse encourages the production of LH rather than FSH, leading to an elevated LH/FSH ratio in women with PCOS. As a result, elevated luteinizing hormone levels trigger the development of metabolic and reproductive problems, including increased androgen synthesis in ovarian theca cells, impaired synthesis of FSH and estrogen, and increased secretion of insulin-like growth factor-1 (IGF-1). Females of reproductive age now frequently suffer from polycystic ovarian syndrome, or PCOS. Since it is a multidisciplinary disorder, managing its symptoms calls for a multidisciplinary consultation. [5]

According to one theory, PCOS is a genetically established ovarian condition where a hormonal injury from increased androgen production in childhood can cause PCOS in adulthood (7–9). Adolescent sheep and rhesus monkeys exhibit numerous signs of PCOS following fetal exposure to elevated doses of androgens. Nevertheless, the cost of using them to investigate the causes of PCOS is unaffordable (10–12). Adiposity may play a central role in generating and maintaining the syndrome. Menstrual regularity is frequently improved by weight loss.

Obesity and fat buildup may be caused by a lipolytic deficiency in sc adipocytes. Furthermore, compared to matched controls, the adipocytes of nonobese women with PCOS are 25% larger. Abdominal sc adipocyte enlargement is a risk factor for type 2 diabetes on its own and is linked to insulin resistance.[6] We and others have investigated the effects and mechanisms of electroacupuncture and exercise in the treatment of PCOS using a rat model in which PCOs are produced by estradiol valerate (17–19). Estradiol valerate causes ovarian shape and acyclicity similar to PCO (16–21), but without the usual metabolic abnormalities of PCOS in humans.

Daily prepubertal testosterone administration for 7–35 days causes PCOS in another promising rat model. The rats exhibited normal PCO shape and most apoptotic follicles, but their insulin and glucose levels were disrupted, suggesting that elevated androgen levels can cause insulin resistance in this paradigm. In 6-week-old female rats, letrozole, a nonsteroidal aromatase inhibitor that prevents testosterone from being converted to estradiol, also causes PCOs. The metabolic features of the condition were not examined, however endocrine abnormalities resembling those in human PCOS were noted.[7]

To better understand PCOS processes and concentrate on therapeutic therapy, PCOS rodent models are created. They are preferred organisms for PCOS research due to their size, lifespan, and physiological similarity. To cause PCOS, several substances are administered to lab animals. DHEA, a common androgen therapy, has been used to induce PCOS-like traits in experimental animals. With it, the pathophysiology of human PCOS is now being studied. Following DHEA administration, female rats and mice develop follicular cysts and experience anovulatory symptoms similar to those of PCOS in humans (7,8). Additionally, through luteinizing hormone, DHEA affects the normal operation of the hypothalamus-pituitary-ovarian axis structure. Although the DHEA-induced PCOS model has limitations because PCOS is also a genetically based disease, it allows for the study and testing of possible biomarkers and treatments for PCOS in women. [8]

Early pubescence is when PCOS develops. The majority of pertinent data, however, has come from clinical research involving adult females, where referral bias is concentrated on examining the more severe traits. Other methods of studying this complicated condition are beneficial, and preclinical models involving animal and in vitro investigations complement clinical evaluation. Neuroendocrine involvement in the etiology of PCOS is highlighted by recent clinical, experimental, and genetic findings.[9]

The luteinizing/follicle-stimulating hormone (LH/FSH) ratio, insulin, growth hormones (GHs), androgens, estrogens, cortisol, parathyroid hormone (PTH), calcitonin, and gonadotropin-releasing hormone (GnRH) are all out of balance in PCOS. These hormones are all involved in bone metabolism, and their imbalance may exacerbate osteoporosis. As a result, this syndrome is also related to faulty bone function.

PCOS is usually diagnosed in women who have trouble getting pregnant. The diagnosis of PCOS usually requires a complete family history, an appropriate laboratory study, and the exclusion of other possible causes of metabolic abnormalities. PCOS has been treated with a variety of therapeutic approaches, such as dietary and lifestyle modifications and the use of drugs like oral contraceptives or antiandrogens. Recently, it has been demonstrated that isothiol treatment is both beneficial and rational in rectifying the endocrine-metabolic issues associated with this illness. [10]

International Journal of Pharmaceutical Research and Applications
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The features of DHEA-induced PCOS models that have yielded thorough understanding of the intricate mechanisms underlying PCOS will be the main focus of this review.

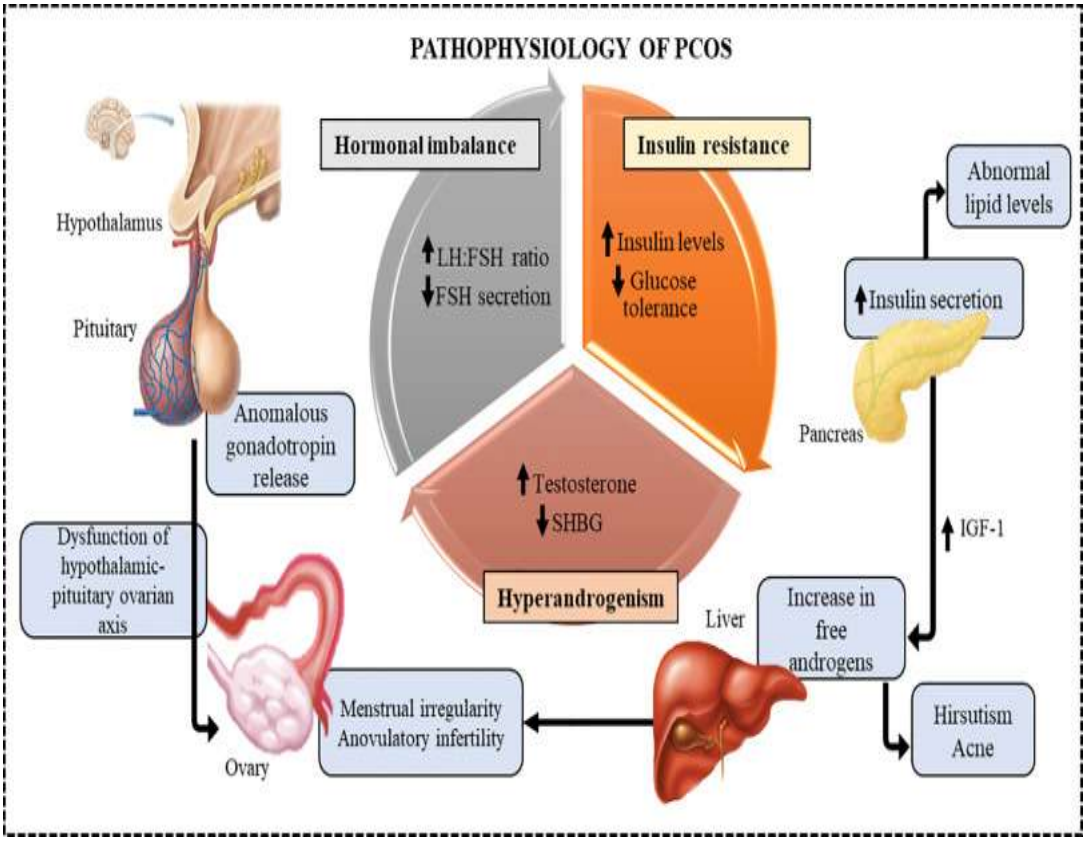

Fig 01: Pathophysiology of PCOS

Phenotypes of PCOS: -

Based on the three main characteristics of PCOS—anovulation, hyperandrogenism, and polycystic ovaries—the medical profession has established four phenotypes that might be considered variations of PCOS. Along an axis of metabolic and ovarian dysfunction, the four phenotypes consistently vary from the most severe (phenotype A) to the least severe (phenotype D) [11].

Feature	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Biochemical/ clinical hyperandrogenism	+	+	+	–
Chronic anovulation	+	+	–	+
Polycystic Ovaries	+	–	+	+

Table 1: Four major clinical phenotypes of PCOS

PCOS Causes:

PCOD is often associated with –

- An unhealthy diet
- A sedentary lifestyle
- Pollution
- Hormone altering medication
- Several OTC (over the counter) medications and supplements

Diagnosis Of PCOS:

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The 1990 National Institutes of Health Science (NIH) US meeting recommended that PCOS should include either hyperandrogenism, anovulation, or both. This suggestion is used to diagnose PCOS. Nonetheless, a 2003 joint ESHRE/ASMR meeting in Rotterdam proposed that polycystic ovarian ultrasonography, in conjunction with hyperandrogenism and anovulation, would be adequate for PCOS diagnosis. In 2006, The Androgen Excess PCOS Society (AEPCOS) provided additional confirmation of this. In addition to being primarily a condition linked to hypogonadism, PCOS is diagnosed by either chronic anovulation or polycystic ovarian ultrasonography.

Criteria for diagnosis of PCOS:

In the same way that women with ovarian cysts may not be diagnosed with PCOS, women with PCOS may not always have polycystic ovaries. In a clinical setting, PCOS-
1.Amenorrhea
2. Sonography
3. Rotterdam criteria (presence of more than two symptoms)

Management Of PCOS:

There is currently no cure for polycystic ovary syndrome. Clinically, the only purpose of the treatment is to control PCOS symptoms (Leena et al., 2016). The hormonal imbalance linked to PCOS cannot be reversed; lifestyle changes are mostly responsible for symptom improvement. At the moment, efforts are done to address PCOS-related symptoms, infertility, or anovulation. Currently, PCOS management options include
1. Allopathic therapy
2. Herbal therapy
3. Lifestyle and dietary modification

Long Term Maintenance of PCOS:

The phrase "maintenance" recognizes that there is currently no known treatment for PCOS. Obesity, oligomenorrhea, and hirsutism frequently make up the main presenting symptoms. Selecting a major metabolic measure to serve as the foundation for first treatment may make sense. The greatest risk factor for diabetes in these women is glucose intolerance, which also stands alone as a risk factor for cardiovascular events. Depending on how well the first treatment works, other targeted treatments for oligomenorrhea and/or hirsutism may be added. If the patient wants to avoid getting pregnant, contraception should be taken into consideration.[12]

Experimental Induction Of PCOS:-
Androgen- Induced PCOS Models

One of the main characteristics of PCOS is hyperandrogenism. It has been proposed that early exposure to high levels of androgens causes PCOS in later life. Therefore, a number of androgens, such as testosterone (T), 5α-dihydroxydrotestosterone (DHT), and dehydroepiandrosterone, have been utilized to cause a PCOS-like syndrome in rodents. It is crucial to remember that research' reporting of ovarian histology and endocrine hormones in various models varies somewhat. Furthermore, the effects of daily androgen injection and/or treatment on physiological indices such body weight, stress indicators, or food consumption are typically not documented, and a number of studies have not evaluated cardiometabolic markers.[13]

Letrozole Induce PCOS

Rats were given letrozole (1 mg/kg) in suspension form (letrozole suspended in 0.5% carboxymethylcellulose (CMC)) for seven weeks to induce PCOS after a week of acclimatization. The dosage was selected in accordance with guidelines recommended in a published paper by Rezvanfar et al. Weight changes were documented weekly during this time, and vaginal cytology—the relative percentage of cornified cells, leukocytes, and epithelial cells under light microscopy—was used to evaluate the estrous cycle every day.The cyclicity of the estrous cycle, the percentage decrease in weight growth, and the restoration of biochemical markers served as the study's exit criterion.

DHEA- induced PCOS models

The adrenal gland is the primary producer of the androgen DHEA. Since DHEA levels are high in women with PCOS, rodents are given DHEA to create PCOS models. A normal proto-col is 6 mg/100 g body weight/day for 20–40 days in a row, beginning on postnatal day 21–23.In mouse models, 7.5 mg 90-day continuous-release pellets have been implanted to administer 25–27 DHEA.The first attempt to create an experimental PCOS model in animals with DHEA application was made in the 1960s. Roy et al. administered various subcutaneous DHEA dosages to female rats.1.5 mg/kg, 3 mg/kg, 4 mg/kg, and 6 mg/kg

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were these dosages. Following treatment, the levels of prolactin, luteinizing hormone, and follicule stimulating hormone were comparable for the 3 mg/kg and 6 mg/kg doses.[14]

Estradiol valerate protocol

Thirty Wistar female rats were split into two groups: the rats in the EV group (n=22) received a single intramuscular injection of 5 mg EV dissolved in 0.5 ml sesame oil, while the rats in the control group (n=8) received a single i.m. injection of 0.5 ml sesame oil.

The dosages were selected in accordance with earlier research that employed letrozole or estradiol valerate to cause PCOS.At the conclusion of the experiment (days 30–32), the rats were sacrificed, and blood, liver, muscle, and POAT were collected for analysis. The ovarian morphology was evaluated by ultrasound under anesthesia with 90 mg/kg ketamine and 10 mg/kg xylazine injected intraperitoneally. An oral glucose tolerance test (OGTT) was also conducted.[15]

T- induced PCOS models

T can cause hyperandrogenism in rats when given either prenatally or after birth. Furthermore, it has been demonstrated that prenatal exposure to T during the crucial fetal development period results in morphological and developmental defects in the reproductive system.19, 20 Pregnant rats were injected with either 5 mg free T on gestational day 20 or 3 mg T daily of T propionate (TP) on days 16 to 19 for prenatal administration.19, 20 Rats received TP injections at a dose of 1.25 mg/100 g body weight at 5 days of age 21 or 1 mg/100 g body weight every day from 21 to 56 days of age. [16]

DHT- induced PCOS models

Since aromatase does not convert DHT into E2, the PCOS phenotype in DHT-treated mice can be examined without taking into account the effects of estrogen derived from androgens.

Prenatal DHT- treated models

Rats were given 3 mg of DHT every day from gestational day 16 to 19, while mice were injected with 250 µg of DHT on days 16, 17, and 18 of gestation 28 to create prenatal DHT-treated animals. The children were used as prenatal models of PCOS treated with DHT.[17]

Genetic remodeling for development of PCOS mouse model

To further understand the molecular underpinnings of PCOS etiopathogenesis, a customized genetically modified animal model or models have been established. Numerous research has effectively developed the concept of familial clustering in PCOS and made it abundantly evident that a person's hereditary predisposition to the condition is rooted in their genetic makeup. Since first-degree relatives of women with PCOS exhibit a significant degree of symptom penetration, it is now generally acknowledged that the disorder is oligogenic. The follistatin locus on chromosome 5, insulin gene variable number tandem repeat, CYP11a, CYP17, CYP19, and a few other important genes may serve as the foundation for focusing on a small number of specific genetic elements in animal models with unique genetic alterations.Because metabolic disorders are often associated with human PCOS, caution should be exercised when choosing suitable transgenic or knockout (KO) animals based only on their ovarian phenotype. The role of ERα in controlling the function of theca cells has been assessed using ERα and/or ERβ knockout mouse models.. Similar to human PCOS, female mice with excess LH/hCG or without plasminogen activator inhibitor-1 (PAI-1) showed hyperplasia of theca cells, hyperandrogenemia, and hyperinsulinemia. In 2009, Dissen et al. showed that transgenic overexpression of the neurotrophin nerve growth factor (NGF), which is a sign of sympathetic hyperactivity, disrupts the 17 α-hydroxylase/C17–20 lyase promoter (17NF mice) and causes ovarian abnormalities that resemble those seen in PCOS-afflicted women's ovaries. At normal levels, NGF helps in follicular growth and ovulation in addition to being essential for the peripheral nervous system's operation.However, in the 17NF animals, an excess of intraovarian NGF causes an intermediate stage of antral follicle growth to be arrested, along with increased granulosa cell death and increased androgen production in response to FSH stimulation. However, follicular cysts did not form, as they only appeared when there was a persistently high plasma LH level. These mice also displayed delayed puberty, irregular estrous cycles, reduced ovulatory response and decreased fertility.In addition to causing infertility, 17NF mice's overproduction of ovarian NGF led to a number of metabolic changes, such as hyperinsulinemia, glucose intolerance, and insulin resistance; an increase in body fat, visceral fat, and lean body mass, which increased body weight; increased bone mineral content and bone mineral density; and systemic sympathetic hyperactivity—

International Journal of Pharmaceutical Research and Applications
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all of which are typically observed in PCOS women. In a 2020 study conducted in Sweden, Manti and colleagues showed that high levels of ovarian NGF hampered the development of the female fetuses during the embryonic stage. These fetuses later showed irregular estrous cycles, changed ovarian expression of steroidogenic markers, and increased systemic sympathetic outflow as adults. In addition, adult 17NF mice acquire liver steatosis, increased fat mass, decreased energy expenditure, and glucose intolerance.Accordingly, the aforementioned research indicates that ovarian sympathetic hyperactivity plays a role in the onset and/or progression of PCOS in women, and that ovarian overexpression of NGF in the mouse model 17NF results in embryonic defects as well as reproductive and metabolic abnormalities in the adult mice that are typical of PCOS in women.Obese New Zealand mice, IR/LepRPOMC knockout mice, Mitoob mice, mice overexpressing human insulin-like growth factor-I (IGF-I), protein kinase B-β (PKBβ/Akt2) KO mice, and Ptenfl/fl–Cyp17iCre (tPtenMT) mice are examples of transgenic mice that exhibit abnormalities in glucose and/or lipid metabolism. These mice typically develop ovarian cysts and metabolic abnormalities.Furthermore, PCOS-like traits are displayed by transgenic mice that have some endocrine system-related genes deleted or overexpressed, such as aromatase KO (Ar KO) mice, hCG-/ LH-overexpressing mice, and inhibin-subunit-overexpressing mice. The majority of the reproductive and metabolic problems linked to PCOS are present in genetically engineered mice models, which may help to solve the enigma of how PCOS develops in women, even though these models may not always accurately reflect the whole spectrum of human PCOS.[18]

Non-Mechanical Models

Zebra fish model –

Zebrafish are a good model to study endocrine systems, reproduction, and transgenerational epigenetic effects because of their quick embryonic development and short life cycle. For a transgenerational epigenetic study, testosterone and dihydrotestosterone (50, 500, or 1000 ng/L) were combined in the egg water of zebrafish embryos either early or late in the postfertilization period to create a fish model of PCOS. By introducing excess androgen during the early stages of embryonic development, this model is utilized to analyze the pathophysiology of the epigenome. The early but not late androgen-exposed F0 generation and the crossover F1 unexposed generation showed alterations in glucose homeostasis and global methylation.

Drasophilla –

All creatures have shown that the development of female gametes is directly impacted by nutritional condition. The Drasophilla model aids in understanding the relationship between PCOS and nutritional status, even if the direct relationship between nutrition and ovarian development is rather unclear regarding the cellular and molecular mechanisms underlying how dietary components affect egg production. Because Drosophila melanogaster has been crucial in resolving this issue because to its extensive and dominant genetic tools as well as its ovarian response to food. With the use of this model, the dietary regulation of oogenesis in Drosophila is understood, and the fruit fly's noteworthy characteristics make it a model for the nutritional regulation of ovarian function. It demonstrates how nutritional status affects gametogenesis, namely ovarian function, which in turn affects reproduction. [19]

Therapeutic options for PCOS:

Oral contraceptives (OCPs):

The OCPs are separated into progesterone-only pills and mixed pills that contain progesterone (norethisterone, desogestrel) and estrogen (estradiol dosage up to 50µg). They are the first line of treatment for women who experience irregular menstruation and do not wish to ovulate. OCPs increase SHBG, which lowers the levels of androgens in the blood.

Antiandrogens:

These medications, which are recommended as first-line treatments for hirsutism, include spironolactone, flutamide, and cyproterone acetate. They work by inhibiting androgen receptors to reduce androgen output.

Insulin sensitizers:

By reducing insulin resistance and restoring normal insulin levels, this class of medications is typically used to treat metabolic co-morbidities linked to PCOS. The menstrual cycle will improve if the IR is reduced because the corresponding testosterone level will also drop. [20]

Ovulation inducing agents:

The most popular medication for treating anovulatory infertile women is clomiphene citrate (CC). By blocking the estrogen receptor via a

International Journal of Pharmaceutical Research and Applications
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negative feedback mechanism, CC raises the level of FSH. [21]

II. CONCLUSION: -

We discussed hormone-induced animal models of PCOS in this review. There are three different types of PCOS animal models: first, second, and third generation. Since they are created by merely imitating the hormonal profiles of PCOS patients, models produced with estrogen and T are regarded as first-generation models. Nevertheless, there are several issues with these models that are resolved in second-generation animal models produced by DHT and letrozole treatment. A variety of clinical symptoms, such as hyperandrogenism, anovulation, and polycystic ovarian morphology, are indicative of PCOS, a complicated endocrine condition. Results from research employing these animal models can offer significant and original understandings of the pathophysiology of PCOS in people.

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No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

DATA AVAILABILITY STATEMENT:
There is no data set associated with this submission

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