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Current Scenario and Recent Advances for the Management strategy and therapeutic outcomes of Polycystic Ovary Syndrome

Sanjeev Kumar
Research Scholar, IEC University, Baddi, Solan, Himachal Pradesh

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ABSTRACT
PCOS, or polycystic ovarian syndrome, is an endocrine condition. Unlike other ovulation diseases, which occur when the ovaries are defective or non-functioning, this syndrome is characterized by prolonged anovulation and ovarian failure. The patient's main complaint is the focus of the majority of therapy at the moment. Reducing symptoms of hyperandrogenism, reestablishing monthly regularity, and achieving pregnancy are the main goals of treatment. Letrozole, an aromatase inhibitor, seems to be a more effective treatment for infertility resulting from polycystic ovarian syndrome than clomiphene citrate, an anti-estrogen and standard infertility medication. It can assist patients in maintaining proper lifestyle modifications, such decreasing body fat, raising metabolism, and improving reproductive health, when given by a multidisciplinary team. The most popular kind of androgen inhibitor for treating menstruation disturbance in PCOS patients who do not wish to become pregnant is compound oral contraceptives. For women with PCOS, losing weight should be their top priority because regular exercise and a healthy, balanced diet may raise insulin sensitivity, speed up metabolism, and safely assist with weight reduction. Their physical health will improve as a result. PCOS symptoms include insulin resistance (IR), metabolic syndrome (MS), and persistent low-grade inflammation in addition to reproductive issues. Recently, there has been progress in our comprehension of the pathophysiological process, diagnosis, and treatment of PCOS.
Keywords: combined oral contraceptive pills, menstrual irregularity, hyperandrogenism, lifestyle interventions, pcos

I. INTRODUCTION

The endocrine condition known as polycystic ovarian syndrome (PCOS) affects many women and is characterized by a variety of symptoms and consequences. Its incidence in all reproductive age groups has been known for decades to range from 8 to 13% [1]. PCOS is distinguished from other forms of ovulation failure by insufficient ovarian follicle formation or decreased gonadotropin production (or both) (not found by normal screening). Anovulation and hypothalamic-pituitary-ovarian axis dysfunction characterize PCOS. It is more common for PCOS individuals to have endometrial hyperplasia. Among the other reproductive symptoms of PCOS are chronic low-grade inflammation, metabolic syndrome (MS), and insulin resistance (IR) [2,3]. Recently, there has been progress in our comprehension of the pathophysiological process, diagnosis, and treatment of PCOS. In this study, we address the treatment and prevention of metabolic comorbidities in PCOS with an emphasis on lifestyle changes, type 2 diabetes (T2DM) medicines, and bariatric surgery.

Pathophysiology of PCOS

The pathophysiology of PCOS is varied and complicated, which is the major reason for the difficulty in comprehending it. The pathogenesis of PCOS has been linked to hyperandrogenism, ovulatory dysfunction, irregular gonadotropin-releasing hormone (GnRH) pulsation and the ensuing abnormal gonadotropin production, and insulin resistance; these variables interact and worsen one another. PCOM is brought on by ovarian dysfunction, which includes hypersecretion of androgens linked to abnormal follicular development and ovulatory failure. [4, 5, 6, 7] By changing the follicular microenvironment and/or GnRH pulsation, high amounts of anti-Müllerian hormone (AMH), which are released by pre-/small antral follicles that accumulate in PCOS ovaries, worsen ovarian failure. The dysregulation of pulsatile GnRH secretion caused by hyperandrogenism can be partially explained by improper progesterone and estrogenic feedback loops, which lead to excessive gonadotropin output, particularly excess LH secretion. [8, 9] The dysregulation of follicular development is made worse by high LH concentrations, which also lead to an imbalance in the LH/FSH ratio and the hypersecretion of androgens from thecal cells. [9,

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10, 11] The pathophysiology of PCOS also includes insulin resistance, but without inclusion in the diagnostic criteria. [12, 13] This insulin resistance is linked to visceral adiposity and adipocyte dysfunction and shows up in insulin-sensitive tissues including the liver and muscle. [11] Excessive androgen secretion raises the level of insulin resistance, and hyperinsulinemia, which results from the insulin resistance, raises androgen secretion even more and causes the liver to produce sex hormone-binding globulin (SHBG), which raises the concentration of bioactive free testosterone in the blood and aggravates hyperandrogenism-related disorders. [15, 16, 17, 18] It is still unclear what caused the vicious circle of illnesses that make up PCOS pathophysiology. The most straightforward explanation for this intricate and varied condition is that insulin resistance initiates PCOS development, whereas hyperandrogenism serves as a predisposing factor. [6, 7, 18, 19, 19] Elevated AMH concentrations aggravate hyperandrogenism, which is brought on by intrinsic malfunction of theca cells and/or the hypothalamus-pituitary-ovarian axis. [8, 9, 10, 11, 20, 21, 23] Insulin resistance leads to hyperinsulinemia, which in turn stimulates androgen secretion by theca cells and modifies the effects of gonadotropins on theca cells. Hyperandrogenism and insulin resistance worsen each other. Excess androgen secretion causes visceral adiposity and adipocyte dysfunction. [14 - 18] Physicians, particularly in East Asia, might be curious in the prevalence of hyperandrogenism in their PCOS patients compared to patients from other ethnic backgrounds. Currently, it may be difficult to detect clinical or biochemical hyperandrogenism, and it is unknown if PCOS patients' phenotypic A–D prevalence differs with ethnicity. Because appropriate cutoff values of the modified Ferriman-Gallway (mFG) score for the definition of hirsutism in ethnic groups with less dense villus hair have not been established, and it is not even clear whether it is appropriate to use the mFG score in these groups for the diagnosis of hirsutism, it is plausible that clinical hyperandrogenism is frequently overlooked in East Asia, where people have less dense villus hair. [3, 22] Currently, tests for direct free testosterone, such radiometric and enzyme-linked assays, which are commonly employed in clinical settings, are not very sensitive or precise, making it challenging to diagnose biochemical hyperandrogenism. [3] Additionally, it should be noted that the presence of high levels of testosterone in the follicular fluid does not always indicate local hyperandrogenism in the ovary. Radioimmunoassay was used to detect normal levels of serum testosterone in two-thirds of East Asian patients with PCOS. [23] Moreover, there are significant differences in body composition amongst ethnic groups, with East Asians exhibiting lower levels of obesity than other races. [3] Nonetheless, patients with PCOS, regardless of fat, have a five-fold greater incidence of impaired glucose tolerance than people without PCOS in Asia, a four-fold higher prevalence in the Americas, and a three-fold higher prevalence in Europe. [13] The diverse character of PCOS and its presentation can be attributed to the combined pathophysiology of hyperandrogenism and insulin resistance, although their individual contributions vary from patient to patient.

Management of PCOS

The symptoms of PCOS in women determine how to treat them. These might be indications of androgen malfunction, menstruation problems, or infertility linked to ovulatory failure.

Weight reduction

There is some evidence, irrespective of body mass index (BMI), that hyperandrogenism associated with PCOS results in central obesity with a high waist/hip ratio. Obesity and anovulation, miscarriage, and difficulties in late pregnancy (including pre-eclampsia and gestational diabetes) are known to be linked.[10, 11] Between 35 and 60 percent of women with PCOS are obese, and this condition is linked to a lack of response or a delayed response to many medications, including gonadotropins, clomiphene citrate (CC), and laparoscopic surgery for surgically treating diathermy. [12] As little as 5% of the starting weight can lead to normalisation of the menstrual cycles and ovulation.[13] Losing weight can improve circulating levels of androgen and glucose, as well as ovulation and pregnancy rates in obese women with PCOS; however, weight loss is only advised for those who are overweight with a BMI > 25–27 kg/m2. Treatment for obesity involves dietary and exercise modifications, medical and surgical procedures, and reproductive therapies; all of these must be carried out during the preconception period and not in conjunction with reproductive therapies.

Diet

Obese PCOS patients are advised to follow low-calorie, low-carb diets; any variation of

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these diets can help these patients lose the 5%–10% of body weight required to restore ovarian function. Reaven (2005) proposed that low-fat diets enhance metabolic effects via reducing hyperinsulinemia.[14]

Exercise

The place of exercise in the management of obese PCOS patients has been the subject of several research. [15] When various diets, whether or not they were linked to exercise, were evaluated, no significant differences were discovered; however, in these individuals, a longer weight loss maintenance period did seem to be connected. Patients with PCOS are advised to increase their physical activity, yet there are frequently restrictions on this. [16] There is a lack of information about the best kind, amount, and frequency of exercise.

Bariatric surgery

It has gained popularity recently as a weight loss method for those who are severely obese. Furthermore, bariatric surgery may be recommended if diet and exercise alone are insufficient to induce natural weight reduction. Two main methods are often used: the Roux-en-Y gastric bypass and adjustable gastric banding. Malabsorptive operations, such as combination and restrictive procedures, are also frequently used. Unsurprisingly, bariatric surgery led to an average weight reduction of 41 ± 9 kg in 12 months and improvements in ovulation, insulin resistance, hyperandrogenism, and hirsutism in 17 women with PCOS and a mean BMI of 50.7 kg/m2.17 All twelve of the PCOS patients who were eligible for follow-up following bariatric surgery for severe obesity had their normal periods returned. [17]. All twelve of the PCOS patients who were eligible for follow-up following bariatric surgery for severe obesity had their normal periods returned. [17] Notably, women who have undergone bariatric surgery are more likely to experience shortages in protein, iron, vitamin B12, folate, vitamin D, and calcium. Nevertheless, opinions on the best ways to test for and supplement with these nutrients are divided.

Ovulation induction

Novovulation in PCOS is associated with low FSH levels and the termination of antral follicle development during the latter phases of maturation. In this procedure, excess LH, androgens, and insulin may act alone, in combination, or both, enhancing steroidogenesis while inhibiting follicular expansion. Anovulatory infertility is the first issue that many women have. The next sections go over medications and other methods that can be used to induce ovulation.

CC

For ovulation induction in these patients, CC is one of the first-line therapies since it is affordable, simple to use, has little side effects, and requires little monitoring.[18] Because CC is an antagonist of the oestrogen receptor, it prevents the estrogen-signaling pathway's negative feedback loop, which raises the availability of FSH. Follicle growth brought on by elevated FSH is followed by an increase in LH and ovulation. those with PCOS and anovulation with normal FSH levels should use CC; however, those with a BMI above 30 and advanced age should not use CC. Legro et al. discovered noteworthy variations in the frequencies of pregnancy between individuals with a BMI > 30 and those with a BMI < 30.[19] Starting on days 3 or 5 of a progestin-induced or spontaneous cycle, doses ranging from 50 to 150 mg are given for a duration of 5 days. In 75%–80% of PCOS individuals, CC causes ovulation; yet, gestation rate approaches 22% each ovulation cycle when measured.20 The antiestrogenic actions of CC, which primarily affect the endometrium and cervical mucus, are responsible for these variations in the results.[18] After using clomiphene for six months, the live birth rate varied between 20% and 40%. Moreover, the bulk of pregnancies happened during the first six ovulatory cycles after therapy started.[19] Hyperstimulation syndrome is uncommon, and the likelihood of multiple pregnancies is less than 10%.

Metformin

The US Food and Drug Administration (FDA) has authorised the biguanide metformin for use as an oral antihyperglycemic medication to treat type 2 diabetes mellitus. Metformin usage is linked to better ovulation, a decrease in circulating testosterone levels, and enhanced menstrual cyclicity.[21] Weight reduction has a positive impact on metabolic benefits, and metformin may even make weight loss more effective. Its main therapeutic effect is to prevent the liver from producing glucose, while it also lowers intestinal glucose absorption and raises insulin sensitivity in peripheral tissues.[22] Metformin probably improves ovulation induction in PCOS-affected women by lowering insulin levels and changing

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how insulin affects the production of ovarian androgen, the development of theca cells, and endometrial tissue. Furthermore, it suppresses ovarian gluconeogenesis, which lowers ovarian androgen production, perhaps by a direct impact.

Numerous dosage schedules have been suggested. [23] Patients are started on 500 mg of metformin daily with meals in order to improve their tolerance. The dosage is raised to 1000 mg for an additional week after the first, and finally to 1500 mg each day. 1500–2550 mg/day (500 or 850 mg three times a day) is the intended dosage. A 1000 mg daily dosage is often required to observe a clinical response. It seems that certain PCOS people respond better to 2000 mg of metformin everyday if they do not respond to 1500 mg. The two most typical metformin adverse effects are diarrhoea and nausea. Patients with sepsis, congestive heart failure, and renal impairment have been reported to have lactic acidosis. Oral hypoglycemic medications have historically been thought to be teratogenic, meaning that using them while pregnant is not advised. Nonetheless, a growing body of evidence indicates that they are safe to take throughout pregnancy. At three and six months of age, Glueck et al. found no significant birth abnormalities or effects on the motor or social development of the newborns. [24] The treated group had a considerably lower incidence of gestational diabetes than the control group of women who did not receive metformin. It's critical to distinguish between two distinct signs in order to pinpoint the precise function of metformin in ovulation induction. Metformin has been seen to increase ovulation rates in naïve PCOS as compared to placebo; however, metformin did not significantly outperform CC in terms of cumulative ovulation, pregnancy, or live birth rates. [25] In patients with naïve PCOS, the combination of metformin and CC is not superior to either CC or metformin alone. [26] When used alone, metformin had no effect on ovulation, pregnancy, or live birth rates in individuals who are resistant to CC; however, when combined with CC, ovulation and pregnancy rates were much higher than when CC was used alone. The likelihood of a live delivery did not increase with combination treatment, though. [27] In PCOS individuals who have developed CC resistance, metformin pretreatment increases the effectiveness of CC. [28] Another insulin-sensitizing medication that has been demonstrated to enhance ovulation and raise pregnancy rates is troglitazone. Nevertheless, it has been taken off the market because of its hepatotoxic effects. [29] In women with PCOS with a mean BMI of 35.5–38.5 kg/m2, rosiglitazone (8 mg/day), another medication in the same class, has been demonstrated to improve both spontaneous and clomiphene-induced ovulation. Though there is currently little research, pioglitazone also seems to be helpful. While there is no short-term risk associated with both pioglitazone and rosiglitazone, there is no proven foetal safety (pregnancy category C of the US FDA recommendations). As soon as a pregnancy is confirmed, they should be stopped if taken. The Cochrane study on insulin-sensitizing medications (metformin, rosiglitazone, pioglitazone, and d-chiro-inositol) for women with PCOS, oligo/amenorrhea, and subfertility was recently revised by Tang et al. They came to the conclusion that metformin is still helpful in enhancing clinical pregnancy and ovulation rates. Nevertheless, there is no proof that metformin increases the number of live births, either whether taken by itself, in conjunction with clomiphene, or in contrast to clomiphene. As a result, it seems that metformin's ability to improve reproductive outcomes in PCOS-affected women is limited. [30]

Aromatase inhibitors

Novel ovulation-inducing drugs that exhibit promise include selective aromatase inhibitors like letrozole and anastrozole. They have great potency and are reversible. Letrozole and anastrozole have a mean half-life of around 45 hours, compared to 5-7 days for CC. Letrozole has undergone far more research to date than anastrozole. [31] Following the emergence of several CC side effects, CC's poor therapeutic outcome, and the intricacy of gonadotropin therapy, letrozole was presented as an assisted reproductive medication. Letrozole increases gonadotropin-releasing hormone (GnRH) and FSH by blocking the hypothalamus-pituitary axis' ability to produce oestrogen. It is thought that women with PCOS have a comparatively lower amount of aromatase, which lowers the number of follicles needed for effective ovulation. Because aromatase inhibitors selectively block the peripheral passage of androgens to oestrogens, they reduce the amount of oestrogens, which causes positive feedback in the pituitary, increases FSH, and optimises ovulation. This relative deficit was taken into consideration when using aromatase inhibitors to induce ovulation. Letrozole has the benefit of promoting monofollicular development without having any peripheral antiestrogenic effects on the

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endometrium.[32] For five days, 2.5–5 mg of letrozole is given. To programme the ovulation, FSH (at the usual dosages for PCOS patients) and hCG (10,000 IU) may also be given when the follicle diameter reaches 18 mm. Pregnancy rates, however, were comparable in a prospective randomised experiment comparing letrozole and clomiphene. Due to potential teratogenicity, Novartis Pharmaceuticals (Basel, Switzerland) has advised against using letrozole for ovulation induction; nonetheless, a comparison with clomiphene did not show an increase in the incidence of major or mild abnormalities.[33]

Glucocorticoids

Ovulation induction has been achieved with the administration of glucocorticoids, such as prednisone and dexamethasone. In CC-resistant PCOS with normal DHEAS, Elnashar et al. showed that inducing ovulation by adding dexamethasone (high dosage, short course) to CC is related with greater ovulation and pregnancy rates in a considerable proportion of patients, without having an unfavourable antiestrogenic impact on the endometrium. [34]

Patients with PCOS who have elevated adrenal androgen may benefit from taking low-dose dexamethasone (0.25–0.5 mg) before bed. [35] The addition of 2 mg of dexamethasone from days 5–14 is linked to a greater ovulation rate and cumulative pregnancy rate, according to a study of 230 PCOS women who failed to ovulate after taking 200 mg of CC for five days. [36]

Trigger factors and drivers for the Pathogenesis of Pcos

For PCOS, a significant degree of family aggregation has been noted. Consistent with the previously mentioned findings, a nationwide register-based cohort research including over 30,000 participants in Sweden revealed that daughters born to women diagnosed with PCOS had a five-fold increased risk of PCOS compared to those born to mothers without PCOS. Furthermore, a Dutch twin cohort study suggested that around 70% of PCOS cases are heritable. [25] More recently, several years following menarche, the incidence of hyperandrogenism, ovulatory dysfunction, and PCOM - all three characteristics of PCOS - was examined in daughters born to mothers with and without PCOS. Of the daughters born to women with PCOS, this was shown to be 16.2% (7/43) but none of the daughters born to mothers without PCOS (0/28) showed all three of these traits. [26] Studies have been conducted on the relationships between different genes and PCOS in an attempt to clarify the mechanism behind the family clustering of PCOS. Genes that control gonadotropin secretion and action as well as ovarian function, such as FSHB (follicle-stimulating hormone B polypeptide), LHCGR (luteinizing hormone/choriogonadotropin receptor), FSHR (follicle-stimulating hormone receptor), AMH, and DENND1A (DENN domain containing 1A), as well as metabolism-related genes like THADA (thyroid adenoma-associated gene) and INSR (insulin receptor), are among the candidate genes suggested by genome-wide association studies (GWAS). [27, 28, 29, 30] Additionally, a comparison of the impact sizes and orientations in the two ethnic groups revealed that the 12 PCOS loci discovered by GWAS in Chinese patients with Northern European ancestry had comparable effects. [31] The discovery of conserved genetic susceptibility factors for PCOS in individuals with European and Chinese ancestry implies that PCOS was prevalent at least 50,000–60,000 years ago, when their ancestors left Africa and subsequently underwent racial divergence. It also suggests a shared genetic risk profile among populations. [32, 33, 34] These results are in line with the lack of variation in PCOS prevalence across individuals of different ethnic backgrounds using the same diagnostic standards [1]. Less than 10% of the high heritability of PCOS is thought to be accounted for by the loci found by GWAS, despite the fact that genetic variables are known to have a role in the disease's pathophysiology. [33, 34] Although the exact processes underpinning PCOS's heritability are still unknown, it is presently thought to have a multifactorial etiology, in which the development of the different PCOS symptoms is driven by the exposure of people with genetic predisposing traits to strong environmental stimuli. [19, 34] The follicular microenvironment, postpartum lifestyle, and prenatal exposure to the intrauterine environment of PCOS-affected women are some examples of environmental variables implicated in the pathogenesis of PCOS. Due to high levels of androgens in the bloodstream and placental anomalies, moms with PCOS experience high concentrations of androgens in the intrauterine environment. [35, 36] The androgen-richness of the intrauterine environment may be made worse by the fetal ovaries' excessive synthesis of androgen in response to the intrauterine environment of moms with PCOS. The aberrant intrauterine environment is further exacerbated in moms with PCOS due to

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hyperinsulinemia caused by metabolic disorders and a high circulating concentration of AMH during pregnancy. [21, 37, 38] Furthermore, a large body of research indicates that women with PCOS have aberrant follicular microenvironments in their ovaries [39] Because of the anomalies in the hypothalamus-pituitary-ovarian axis and cal cell activity, this is also hyperandrogenic. [9, 10, 11, 20] Because pre- and tiny antral follicles, which release AMH, are more numerous and have different functions, the concentration of AMH in the area is high. [40, 41, 42, 43] One important characteristic of PCOS is low-grade systemic inflammation together with a proinflammatory condition in the follicular milieu. Moreover, PCOS is characterized by ER stress and local oxidative stress. [45, 46, 47, 48] The vicious cycle of oxidative stress, ER stress, and inflammation damages the PCOS ovary's follicular milieu. Local hyperandrogenic circumstances exacerbate this effect. Furthermore, aberrant metabolism, such as hyperinsulinemia, negatively impacts the follicular microenvironment. 45, 49, 50, 51, 52, and 53] Women diagnosed with PCOS also have a buildup of exogenous toxins in their ovaries, such as advanced glycation end products (AGEs) and endocrine-disrupting chemicals (EDCs). [54, 55] The Maillard reaction, a non-enzymatic interaction between the main amino groups of proteins and the carbonyl groups of carbohydrates, results in the production of AGEs. Without a doubt, the pathophysiology of PCOS is driven by an adverse lifestyle, which includes a bad diet that also raises the risk of metabolic illness. [11, 19] The development of PCOS may also be influenced by certain lifestyle choices that cause exogenous toxins to accumulate in the follicular environment, such as eating foods high in AGEs and being exposed to EDCs. Although AGEs can develop endogenously or exogenously, the majority do so as a result of smoking or eating a diet heavy in fat and/or protein, particularly if that diet includes foods cooked at a high temperature and low moisture content. [56]

Role and responsibilities of follicular Er Stress in the Pathophysiology of Pcos

ER stress - It has recently come to light that ER stress is crucial for both the maintenance of physiological systems and the development of many illnesses. The secretory protein folding and assembly process takes place in the ER, which is the organelle in charge of this process. ER stress is characterized by the build-up of unfolded or misfolded proteins in the ER as a result of an imbalance between the ER's capacity to fold proteins and the demand for it. [49, 53, 57, 58] The unfolded protein response (UPR), which is the collective name for the signal transduction cascades activated in response to ER stress, impacts and modulates a range of cellular processes. The UPR essentially functions to maintain the life of the cell and restore homeostasis in three ways: by decreasing protein translation; by boosting the synthesis of ER chaperones and so increasing the capacity to fold proteins; and by producing ER-associated degradation (ERAD) factors that eliminate irreversibly misfolded proteins. On the other hand, programmed cell death is induced by the UPR if the ER stress cannot be alleviated. In humans, ER stress and the UPR are important in a number of pathological disorders, including as diabetes, neurodegeneration, cancer, inflammatory diseases, and fibrosis. [49, 59].

ER stress in PCOS - Gonadotrophins and intraovarian factors coordinate their geographical and temporal regulation of the follicular milieu. Intraovarian factors are important in pathological disorders of the ovary, such as PCOS, and have regulatory roles throughout the whole process of follicular development. [39, 53, 60, 61] For the first time, we showed that ER stress pathways are activated in the granulosa cells of both humans and a mouse model of PCOS caused by continuous androgen injection; other labs have also corroborated this discovery. [48–52, 62, 63, 64, 65, 66, 67] Additionally, we discovered that local hyperandrogenism in the PCOS follicular milieu activates ER stress in human granulosa cells [52, 53], and mice granulosa cells have corroborated this observation. [63] In addition to oxidative stress and local inflammation, which are closely related to ER stress and create a vicious cycle, local hyperandrogenic conditions may also be activators of ER stress in the follicular milieu of PCOS. [45, 49–53] The activation of ER stress may also be explained by the accumulation of AGEs and lipids in the PCOS follicular milieu. [68, 69] ER stress may be triggered by a combination of local variables that are increased in the follicular milieu of PCOS, compromising ER function. A failure of dominant follicle selection to ovulate, an ovulatory abnormality, and aberrant follicular development that increases in the early stage and stops at the antral stage are the hallmarks of ovarian dysfunction in PCOS. [70] Patients with PCOS are classified as having PCOM with interstitial fibrosis in their ovarian morphology. [71] We showed that

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several functional changes in granulosa cells caused by ER stress contribute to the pathogenesis of PCOS [48, 52, 53, 72, 73, 74]. ER stress causes granulosa cells to produce more of the profibrotic growth factor transforming growth factor-β1 (TGF-β1), and thus speeds up the ovary's interstitial fibrosis, a sign of PCOS. [48] ER stress is linked to follicular development halt during the antral stage, another feature of PCOS, and promotes the testosterone-induced apoptosis of granulosa cells by inducing the proapoptotic factor death receptor 5 (DR5). [52] Additionally, ER stress causes the expression of the receptor for advanced glycation end products (RAGE) in granulosa cells, which is stimulated by testosterone and leads to the buildup of AGEs in these cells. [72] Patients with PCOS are known to have an accumulation of AGEs in their granulosa cells, which are linked to the disease. [75] Additionally, in granulosa cells, ER stress activates the aryl hydrocarbon receptor (AHR), a typical receptor for EDCs, and its downstream signaling, which suggests that ER stress may modify steroid metabolism in these cells. 73 Furthermore, Notch signaling, one of the most evolutionarily highly conserved signaling systems, which regulates various cellular processes via juxtacrine cell–cell interactions, induces the expression of multiple genes associated with cumulus oocyte–complex (COC) expansion in granulosa cells in response to ER stress. 76 The ER stress-notch route is responsible for the increased growth of COCs, as demonstrated by their diameter measurements. However, it is unclear if this hypermaturity of COCs contributes to the ovulatory failure that is characteristic of PCOS. 74

Clinical implications - These results imply that the UPR and ER stress are viable PCOS treatment targets. In fact, administering ER stress inhibitors to mice with PCOS caused by dehydroepiandrosterone (DHEA) improves their reproductive dysfunction; particularly, it decreases the amount of atretic antral follicles, improving the estrous cycle and PCOM. 72 According to histology, ER stress inhibitor therapy lowers the ovary's levels of interstitial fibrosis and collagen deposition, as well as the granulosa cells' apoptosis, buildup of AGEs in these cells, and ovarian ER stress. [48, 52, 72]

Targeting certain UPR components is one way to modulate ER stress and the UPR; the other is to lessen ER stress by reducing the underlying protein misfolding. 53 Chemical chaperones can be employed as a pharmaceutical method for the first strategy, and lifestyle changes might also work well. A class of low-molecular-mass substances known as chemical chaperones stabilizes protein folding and inhibits aberrant protein aggregation, which lowers protein misfolding. 77 Recent investigations have demonstrated the activity of two chemical chaperones that have long been used therapeutically to treat liver illnesses and urea cycle problems, respectively: tauroursodeoxycholic acid (TUDCA) and 4–phenylbutyrate (4–PBA). Lifestyle has a direct or indirect correlation with the activation of ER stress. For example, obese women's granulosa cells have active ER stress. 78 Furthermore, it is intimately linked to other local characteristics influenced by lifestyle, such as inflammation, AGEs, and oxidative stress. 68, 79 Given that lifestyle modifications, like as taking supplements, are often approved as components of preconception care, they could be useful strategies. Conversely, at this time, there are no small compounds being used in therapeutic settings that specifically target UPR factors. There are several intriguing compounds being developed, specifically aimed against the UPR branch that is triggered by double-stranded RNA-activated protein kinase-like ER kinase (PERK). 59

Prenatal Exposure to Excess Androgens, Alterations in the Gut Microbiome, and the Development of Pcos

Girls whose mothers with PCOS are exposed to high levels of androgens throughout pregnancy. The anogenital distance, a biomarker of intrauterine exposure to excess androgens during the fetal and neonatal periods as well as in adulthood, is bigger in daughters born to mothers with PCOS. 80, 81, 82, 83 Furthermore, during pregnancy, women with PCOS had greater serum testosterone concentrations than women without it. 36, 84 Additionally, compared to women without PCOS, placental tissue from PCOS patients exhibits higher 3β-hydroxysteroid dehydrogenase-1 (3β-HSD-1) and lower P450 aromatase activity. These findings may help to explain why pregnant PCOS patients experience a hyperandrogenic intrauterine environment. 36 These results support a role for increased androgen exposure during pregnancy in PCOS-affected women's daughters. Pregnant PCOS women may have a hyperandrogenic intrauterine environment due to a number of additional factors. Fetal hyperinsulinemia, or an increase in androgen synthesis from the ovaries of the fetus after midgestation, can be caused by metabolic malfunction in women with PCOS. 37, 38

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Furthermore, AMH-treated pregnant mice showed reduced placental testosterone metabolism to estradiol and increased maternal neuroendocrine-induced testosterone excess, which may lead to hyperandrogenism in utero. Pregnant women with PCOS also had higher serum AMH concentrations than women without the condition. 21 As previously discussed in-depth, a multitude of research have demonstrated that adult rats, lambs, and rhesus monkeys who were prenatally androgenized (PNA) display reproductive and metabolic characteristics resembling those of PCOS. 85, 86, 87 The process by which exposure to androgens during pregnancy might lead to the development of PCOS in adulthood is still being studied. The production of epigenetic modifications in fetal somatic and/or germ cells as a result of prenatal androgen exposure is one theory. Specific epigenetic modifications are brought about in the ovary, especially in the granulosa and theca cells, as well as in the major metabolic tissues, such as the liver, muscles, and visceral and subcutaneous adipose tissue, by exposure to androgens during pregnancy. 88, 89 Germ cell epigenetic alteration may also be induced by prenatal androgen exposure: The granddaughters of female mice exposed to androgens during perinatality and those exposed to AMH, which induces intrauterine hyperandrogenism, have reproductive and metabolic features similar to PCOS. 24, 90 It's also conceivable that exposure to androgens during pregnancy might result in aberrant ovarian and early follicular development. Compared to daughters of mothers without PCOS, daughters of PCOS-affected mothers had higher blood concentrations of AMH, which is generated by granulosa cells and represents follicular growth during infancy, prepuberty, and the time of birth. 35, 91 Furthermore, women with PCOS have ovaries that have a high density of tiny preantral follicles. This might be due to either a higher population of germ cells in the fetal ovary or a reduced rate of oocyte loss during late gestation, childhood, and puberty. 92 The dysbiosis of the gut microbiota in adult female mice exposed to androgens during pregnancy is another intriguing observation that may relate prenatal androgen exposure to PCOS in later life. 93 , 94. Over the past 10 years, more and more research has been done on the connections between different physiological and pathological diseases and the gut microbiota. This branch of study is particularly interested in metabolic illnesses, and growing data points to the significant and causal roles that gut microbiome dysbiosis plays in metabolic disorders including type 2 diabetes and obesity. 95 and 96 Considering the correlation between the amounts of sex steroid hormones and the makeup of gut microbes, 97, 98 it is plausible that modifications to the gut microbiome might contribute to the pathogenesis of PCOS. According to a recent study, current research has shown that the gut microbiomes of adult PCOS patients and different PCOS models differ from those of healthy people and control animals, respectively. 99 Furthermore, the PCOS-like characteristics of such mice are ameliorated by cohousing with or transplanting feces from healthy rats. These results suggest that the pathophysiology of PCOS involves the gut microbiota as a causal factor. 101, 100 It is postulated that high levels of androgen exposure during pregnancy might cause early gut microbiome dysbiosis, which could subsequently result in the development of PCOS. To investigate this hypothesis, we first compared the gut microbiomes of PNA mice that were induced by injecting dihydrotestosterone (DHT) into pregnant dams and control mice at four weeks of age, six weeks during puberty, eight weeks during adolescence, twelve weeks during young adulthood, and sixteen weeks during adulthood. Next, we looked at the time correlation between the changes in the gut microbiota and the emergence of phenotypes resembling PCOS. 102 Estrous cyclicity, ovarian histology, and serum testosterone concentration were used to identify the PCOS-like reproductive phenotype, while body mass, visceral adipocyte size, insulin tolerance, and fasting blood glucose (FBG) concentration were used to evaluate the metabolic phenotype. To describe the gut microbiomes of mice, we used next-generation sequencing (NGS) of fecal bacterial 16S rRNA genes. The differences in the bacterial taxa between the control and PNA offspring were also determined, as were the α- and β-diversities, which indicate the richness of the microbial species and the similarity between the groups, respectively. We discovered that in PNA offspring 102, problems start to show up in the gut microbiota as early as or even before PCOS-like traits occur. In particular, the PNA offspring's reproductive phenotype was visible around puberty, while the metabolic characteristics of PCOS were seen in early adulthood. On the other hand, changes in the makeup of the gut microbiome of female PNA offspring were evident even before puberty and persisted throughout the investigation. PNA offspring showed a decreased diversity of bacterial

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taxa beyond young adulthood, and during adolescence, there were notable distinctions between the microbial communities in the PNA and control groups. Nine out of the eleven bacterial taxa had lower abundances in the PNA group, and the PNA group consistently had higher or lower abundances of these taxa at various time periods. Furthermore, before to and throughout puberty, the abundance of five and ten of these eleven taxa was already lower, respectively. Our findings suggest that female PNA offspring who are susceptible to PCOS already have an abnormal gut microbial composition soon after weaning, and this may be amplified by the consumption of certain foods and sex steroid action after puberty, contributing to the development of the reproductive and metabolic phenotypes of PCOS. Additionally, abnormalities appear in the gut microbiome as early as or even before PCOS-like phenotypes manifest in PNA offspring, and these mimic the in utero environment of women with PCOS. Crucially, our results offer a unique approach to the prevention of PCOS in later life, as there is presently no preventative method for usage in girls with a high risk of subsequently acquiring PCOS, especially for the daughters of mothers with PCOS. Intervention studies are required to elucidate the role of gut microbiome modifications in the development of PCOS in later life. Furthermore, figuring out the mechanism that causes dysbiosis in PNA kids as soon as they are weaned could help determine whether PCOS pregnant women or their daughters would benefit more from therapies. Changes made to PNA mothers' intrauterine environments may have an impact on how their pups' gut microbiomes develop. Alternatively, DHT therapy may modify the gut, skin, and/or milk microbiome of PNA mothers, and this modified microbial community may be passed on to their pups during birth and nursing. Moreover, determining which fecal metabolites in PNA children are impacted by dysbiosis might aid in directing the creation of innovative pre-, pro-, and postbiotics that could potentially avert the onset of PCOS.

II. CONCLUSIONS

In general, compared to women without PCOS, women with PCOS have a higher risk of obstetric, cardiovascular, metabolic, and psychological issues. These hazards can vary over a person's life and are not always present in PCOS individuals. PCOS characteristics appear to be closely associated with this variability. It is unclear, therefore, exactly whatever pathogenetic process connects PCOS to the increased incidence of both short- and long-term problems. Though their precise mechanisms of action are still unclear, the same PCOS-associated hormonal and metabolic features—such as visceral obesity, IR and accompanying hyperinsulinemia, and hyperandrogenism—play a critical role in raising these risks. Race has an impact on PCOS since there are ethnic variations in both the metabolic phenotype and societal models of behaviour. These variations probably contribute to the many ways that PCOS manifests itself, which have an impact on these women's quality of life and have long-term effects.

While all women experience an increase in insulin resistance (IR) and abdominal obesity with ageing, and their cardiometabolic profile deteriorates after menopause, women with PCOS appear to stabilise or improve in certain metabolic risk factors during the menopausal transition (e.g., in LDL cholesterol levels or glucose tolerance). There are currently insufficient and inconsistent results from well-designed longitudinal follow-up studies that compare PCOS individuals with healthy women from early reproductive age to menopause. Even while women with PCOS exhibit better menstrual cyclicity and a significant drop in testosterone levels, nothing is known about how these women transition into menopause and what PCOS phenotypes they may have in the postmenopausal stage. Given these factors, screening for obstetric, cardiovascular, and metabolic risk factors should be performed on all women diagnosed with PCOS. However, it is also critical to take into account the heterogeneity of the syndrome, which can arise from patient age as well as various hormonal, reproductive, and ethnic characteristics. Unfortunately, precise diagnostic criteria based on distinct age groups or based on specific ethnic background are not currently available. More investigation is required to enhance the diagnostic procedure in order to choose a particular course of treatment, personalise the therapy, and make lifestyle adjustments.

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