2025

Dysregulation in polycystic ovary syndrome: mechanisms and therapeutic approache

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

DYSREGULATION IN POLYCYSTIC OVARY SYNDROME: MECHANISMS AND THERAPEUTIC APPROACHES

by

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B.S., Indiana University, 2023

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2025

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ACKNOWLEDGMENTS

I would like to thank my friends and family for their unwavering love and support. Without their support, this thesis would not have been possible.

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Berrie Benjamin

ABSTRACT

Polycystic ovary syndrome (PCOS),a complex widespread hormonal disorder that affects between 8-13% of reproductive-aged women globally. It is marked by high levels of androgens (male hormones), irregular ovulation, and metabolic disorders, all of which are linked to disruptions in gonadotropin regulation. The hypothalamic-pituitary-gonadal (HPG) axis plays a key role in reproductive function, controlling the release of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle- stimulating hormone (FSH). Women with PCOS, experience irregular GnRH signaling that leads to an overproduction of LH and a reduction in FSH, which in turn stimulates excessive androgen production and hinders proper follicle development. Insulin resistance, another common feature of PCOS, further disrupts hormonal balance by amplifying androgen synthesis. Currently, PCOS treatments focus on managing symptoms through hormonal therapies, insulin-sensitizing medications, and lifestyle changes. However, current research is moving beyond symptom management toward potential long-term solutions. New approaches under investigation include stem cell therapy, gene-targeted treatments, kisspeptin-based therapies, and interventions targeting the gut microbiome. While PCOS does not yet have a cure,scientific advancements are bringing the possibly of personalized, lasting treatments closer to reality. This thesis examines the role of gonadotropins

reproductive health, their connection to PCOS, and the promising research shaping the future of treatment.

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LIST OF ABBREVIATIONS

AA ..... Adrenal Androgen

ACTH ..... Adrenocorticotropic Hormone

AE-PCOS ..... Androgen Excess & PCOS Society

AMH ..... Anti-Müllerian Hormone

CRP ..... C-Reactive Protein

DHEA-S ..... Dehydroepiandrosterone Sulfate

DHT ..... Dihydrotestosterone

DOGMA ..... Dysbiosis of Gut Microbiota

FSH ..... Follicle-Stimulating Hormone

FSHR ..... Follicle-Stimulating Hormone Receptor

GnRH ..... Gonadotropin-Releasing Hormone

HPG ..... Hypothalamic-Pituitary-Gonadal

IL-6 ..... Interleukin-6

INSR ..... Insulin Receptor

iPSCs ..... Induced Pulripotent Stem Cells

LH ..... Luteinizing Hormone

LHCGR ..... Luteinizing Hormone/Choriogonadotropin Receptor

MSC ..... Mesenchymal Stem Cells

NIH ..... The National Institutes of Health

PCOS ..... Polycystic Ovary Syndrome

Phenotype A ..... Classic PCOS

Phenotype B ..... Metabolic PCOS

Phenotype C ..... Ovulatory PCOS

Phenotype D ..... Mild PCOS

RNAi..... RNA Interference

SHBG..... Sex Hormone-Binding Globulin

TNF- α ..... Tumor Necrosis Factor-Alpha

UC-MSCs..... Umbilical Cord Mesechymal Stem Cells

CHAPTER ONE: INTRODUCTION

Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS)is the most common hormonal disorder in women of reproductive age, yet it is poorly understood. PCOS can cause infertility, metabolic problems such as insulin resistance and obesity, and cardiovascular diseases in women (1). PCOS was first described in medical literature in the early 1930s,then in 1935 the condition was formally recognized and given its name by scientists Irving Freiler Stein and Micheal Leventhal (1).They described the syndrome as having ovarian cysts accompanied by anovulation , which is a condition where ovaries do not release eggs during a menstrual cycle (1).

In 1968, scientists first suggested that PCOS could be linked to genetics, meaning that it could run in families. Researchers discovered that in many families, around 55-60% of women with PCOS had close relatives such as a sister or a mother who also had the condition (2). Initially, many scientists believed that PCOS was inherited through autosomal dominant inheritance (1,2). However, later research showed that PCOS is a very complicated disorder, that affected by multiple different genes and not caused by just one inherited trait (2,3). In 1995,at an outpatient clinic in Australia, scientists studied with 34 sets of twins, to understand how much of a role genetics plays in PCOS. Out of the 34 sets of twins, 19 were identical meaning that they shared 100% of their genes, and 15 were fraternal twins

meaning they shared about 50% of their genes. The authors used to determine if twins had PCOS were ultrasounds, lab tests, and physical exams. The results showed that in 19 identical twin pairs, PCOS was present in both twins in 14 cases and in only one twin in 5 cases. Among the 15 fraternal twin pairs, PCOS was present in both twins in 9 cases and in only one twin in 6 cases (3).

These results suggested that PCOS is not purely genetic, but other factors like environment and lifestyle, also play a role. It is now thought that PCOS is an X-linked polygenic disorder, this means that genes on the X chromosome may contribute to PCOS, alongside many other genetic factors (3). From 1935 until the late 1970s, research on PCOS mainly focused on the endocrine causes. Then, in the last two decades of the 20th century, scientists began to focus more closely on the metabolic issues in PCOS (1). Recently, new research done in molecular biology has offered a new insight into the condition's underlying causes.

Diagnosis Challenges and Epidemiology

The diagnosis of Polycystic ovary syndrome (PCOS) is a very controversial topic in clinical endocrinology. Given that the condition manifests itself in different ways in different women, together with its complex pathophysiology physicians are unable to fully understand and diagnose the disorder. Rotterdam criteria, descriptive definition for PCOS, were developed in 2003 to determine diagnosis. Accordingly, 2 out of these 3

conditions must be met in order to be diagnosed with PCOS: 1) irregular or missing periods, 2) having high levels of male hormones, and 3) each polycystic ovary has to have at least 12 cysts that are between 2–9 mm in size (4). However, some concerns were raised about this diagnostic criteria, for one young girls often have irregular menstrual cycles during the early stages of puberty, so doctors should carefully assess their symptoms before diagnosing PCOS. Another reason is that ultrasounds to check for ovaries are not usually done on teenage girls, so there is usually no immediate attention to confirm the presence of cysts (4). When an ultrasound exam is finally done, it is common for teenage girls to have ovaries filled with small follicles, so it is difficult to determine what is normal and what is a sign of PCOS until later in life (4).

A woman's ovaries generally have significantly fewer follicles as they approach menopause age range which typically occurs around their mid to late forties, with the most noticeable decline in follicles occurring after the age of thirty-five (4). Given these challenges the Pediatric Endocrine Society has created special guidelines in order to help physicians be able to diagnose PCOS in a more timely and accurate manner in both teens and adults (4). The appropriate consensus is depicted in the table below (Table 1).

Table 1-The table above shows the different diagnostic guidelines for early diagnosis and management of PCOS, based on age-specific and stage-appropriate standards, in order to identify persistent hyperandrogenic oligoanovulation (4).

Supplementary Table 1.

Differential diagnostic guidelines for diagnosis of polycystic ovary syndrome in adults and adolescence

Adult	Adolescence
Phenotype I: NIH criteria	AUB
Clinical and/or biochemical HA	Abnormal for age
Oligoanovulation	Persistent symptoms for 1-2 years
Phenotype II: RC	HA
Clinical and/or biochemical HA	Persistent testosterone elevation above normal levels
Polycystic ovary	Moderate-to-severe hirsutism
Oligomenorrhea/amenorrhea	Moderate-to-severe acne vulgaris to indicate HA
Phenotype III: AES	
Clinical and/or biochemical HA	

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AUB=Abnormal uterine bleeding, HA=Hyperandrogenism, NIH=National Institutes of Health, RC=Rotterdam criteria, AES=Androgen excess society

Despite PCOS impacting public health, scientists and physicians still don't have clear or consistent data on how many women are affected and exactly how many new cases of PCOS occur each year. To ameliorate this, a study on women members of the Kaiser Permanente Washington ranging from of 16 to 40. The researchers analyzed the medical records of these women to between the years 2006 and 2019 to track how many new cases were identified over time (5) The participants needed to be enrolled at Kaiser Permanente for a minimum of 3 years. Women whose ovaries or uterus that had been removed, were excluded from this study. The authors

found that out of 177,527 women, 2,491 new cases of PCOS were diagnosed (5). The average age of diagnosis was 26.9 years old and the average body mass index(BMI) was 31.6, which is the range for obesity. Overall, about 42.5 out of 10,000 women were diagnosed with PCOS per year (5). The rate at which women were diagnosed with PCOS for the most part stayed the same, however it was discovered that in younger women between the ages of 16-20, the PCOS cases were increased from 31.0 to 51.9 per 10,000. However, PCOS cases decreased in women between the ages of 26-30, going from 82.8 to 45.0 per 10,000 (5).This research shows that the number of new cases of PCOS per year remain stable, however more younger women are being diagnosed. A, possible being that doctors are becoming more aware of PCOS's long term-term health risks and are diagnosing it earlier and more often than in the past. This may be attributed to increased awareness of the condition rising obesity rates (5).

The authors of the study noted that there was a slight decrease in PCOS diagnosis among non-Hispanic white women. Among the white women in the study in 2019, 5.2% had PCOS , with the highest rates in Hawaiian or Pacific Islanders at 7.6%,followed by Native American and Hispanic women (5). In a different study conducted in the United States that involved 400 women ranging from 18-45, it was noted that 4% of both black and white women have PCOS. In European countries such as Greece, Spain, and the UK about 6.8% of women with

PCOS. In China had 5.6% of women diagnosed with PCOS, in India 9.13%, and in Pakistan the highest percentage, 40-50% of women were diagnosed with PCOS (6) .This study shows that the condition is common worldwide , with the highest percentage of women affected in South Asian populations. The difference in PCOS prevalence across different populations could be due to several factors such as diet, lifestyle, and healthcare access. Also, some studies could be using different criteria to diagnose PCOS, which can also explain the variations in reported numbers.(6)

Gonadotropin Dysregulation in PCOS

The disorder is still underdiagnosed with many cases going unnoticed. A common issue in PCOS is that it is harder for women to get pregnant presumably due to irregular menstrual cycles (7). At the core of this issue is a hormone called gonadotropin-releasing hormone (GnRH), which acts like the main control center for the reproductive system. Normally, GnRH is released in a steady pattern, which helps control the levels of two key hormones known as Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH). LH stimulates ovaries to release eggs, and FSH is required for proper eggs develop properly (7). In women with PCOS, the body's natural pattern gets disrupted. Instead of following the normal rhythm, GnRH gets released too often, which in affects the balance between LH and FSH (7). This leads to very high levels of LH being created and low levels of FSH, making it harder for ovaries to release eggs and causing high levels of androgens (male hormones) to be present (7).

High levels of LH signals to the ovaries to release more androgens than usual, which can cause acne, extra hair growth, and ovulation problems. Too little FSH result in inability of the follicles to develop properly, making it harder for eggs to mature and be released. This can lead to irregular periods and the formation of cysts in the ovaries (8). Scientists are unable to fully understand why GnRH behaves this way in PCOS, but there is ongoing research that is aimed at explaining the causes (9). It is important to note that the reason PCOS remains a major health concern goes beyond reproductive health. PCOS is associated with metabolic syndrome, which is linked to high risk of developing cardiovascular diseases, high blood pressure, and type two diabetes (9).PCOS can also cause psychological effects such as depression, anxiety, and negative body image. This can lead to social stigma , which can cause an effect on an individual's relationships, work, and lifestyle (9).Since PCOS is not just a reproductive or hormonal disorder, it has significant effects on mental health, body image, and relationships. Research has shown that up to 50% of women with PCOS experience clinically significant depression and anxiety due to a number of factors: a)excessive hair growth, and hair thinning, which can impact self-esteem, b)irregular cycles and infertility, leading to emotional distress, c) Weight gain and insulin and skin tags, which contribute to body image struggles (4,10,11,18,).Another effect that PCOS has that has been studied extensively is sexual dysfunction. Sexual dysfunction is 2-3 times more common in women with PCOS due to: a) Hormonal imbalances that reduce libido, b) Body

dissatisfaction that affects sexual confidence, c) Mood disorders can interfere with intimacy (4,10,11,18,) .

Thesis Objectives

The objective of this thesis is to take an in-depth look into gonadotropin dysregulation in PCOS, and how this affects the body, the pathophysiology of PCOS, and metabolic dysfunction. Specifically, it will analyze how disruptions in hormonal mechanisms, such GnRH pulsatility and LH/FSH imbalance, contribute to PCOS. It will also examine the relationship between hyperandrogenism and insulin resistance, showing how metabolic dysfunction causes reproductive symptoms to worsen. This thesis will discuss new research in genetics, epigenetics, and gut microbiome could lead to potential new treatment outcomes. Finally, it will also review current and future treatments ranging from medication to regenerative medicine, offering insight on how these new developments could affect future management of PCOS.

CHAPTER 2: NORMAL GONADOTROPIN PHYSIOLOGY

The hypothalamic-pituitary-gonadal (HPG) axis plays a central role in regulating reproductive function by releasing and responding to the hormonal signals that regulate ovarian function. It is this axis that regulates reproduction through the synthesis and secretion of gonadotropin hormones such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), through a complex feedback system that involves the hypothalamus, pituitary gland, and gonads(gland producing hormones such as testes and ovaries) (10). This controlled regulation of hormones ensures correct follicular development, ovulation, and menstrual cycle maintenance. The hypothalamus, which is in the brain, plays a crucial role in reproductive function. It releases gonadotropin-releasing hormone (GnRH) in a pulsatile manner, which stimulates the anterior pituitary gland to release LH and FSH, both are key hormones in the menstrual cycle, ovulation, and ovarian function (10).

Any disruption to the HPG system can lead to hormonal imbalances that affect fertility and cause hyperandrogenic symptoms. The precise frequency and amplitude of GnRH pulses are extremely important, as they determine the relative levels of the gonadotropin hormones, which directly control ovarian function. Any changes to this system can cause significant reproductive issues pathologies. In normal regulation, the ovaries release progesterone and estrogen, which provide feedback to the hypothalamus and pituitary to control GnRH pulsatility, therefore, maintaining hormonal balance (10,11). In the early follicular phase of a

menstrual cycle, low levels of estrogen provide negative feedback, which in turn leads to a decrease in GnRH pulses (11). Slow GnRH pulses favor the release of FSH, which promotes the growth of ovarian follicles. As estrogen levels rise and the follicle matures, a positive feedback mechanism
increases the frequency of GnRH pulses, promoting LH secretion, which triggers ovulation. After ovulation, the ruptured follicle is converted into the corpus luteum, which releases progesterone (11).

Progesterone is secreted to help maintain hormonal balance through a negative feedback mechanism on the hypothalamus and pituitary, thus reducing the secretion of GnRH, LH, and FSH (10,11). This ensures that the cycle continues in an organized manner, preparing the endometrium for a potential pregnancy. If fertilization does not occur, progesterone and estrogen levels decline, removing the negative feedback on the HPG axis and allowing a new cycle to begin.

However, when a woman has PCOS, the normal secretion of GnRH is disrupted. In individuals with PCOS, the pulse frequency of GnRH becomes elevated, resulting in an imbalance in LH and FSH levels (10,11). This leads to excessive LH and decreased FSH levels, which, results in hormonal imbalances leads to abnormal problems with ovulation, irregular periods, and excessive hair growth.

The ovaries are crucial in the regulation of female fertility, as they are where egg development occurs and are also responsible for producing estrogen and progesterone. Their function is largely dependent on the interactions between granulosa and theca cells within the developing follicles (11,12). Theca cells, which surround the developing oocyte, are
responsible for producing androgens, which are then converted into estrogen by granulosa cells. The Interdependent relationship between these two cell types is known as the two-cell, two-gonadotropin model. In this model, LH stimulates the theca cells to produce androgens, which are then converted into estrogen under the influence of FSH by granulosa cells (11,12).

Under normal reproductive conditions, in every menstrual cycle, a group of antral follicles are recruited to grow by FSH. As the follicles grow, one becomes the dominant follicle. This follicle continues to mature and eventually releases an egg in the process of ovulation. The egg being released is due to a surge in LSH (7,810,11). However, in PCOS, this process is often disrupted. When there is an increased level of LH with low levels of FSH, the follicles are unable to mature properly,

resulting in underdeveloped follicles (7,8,10,11). This often leads to the formation of multiple cysts in the ovaries. This dysfunction causes ovulation failure, leading to infertility and other symptoms leading to PCOS (7,8,10,11).

PCOS can have metabolic effects beyond reproduction. Many women with PCOS experience insulin resistance, a condition in which cells do not respond properly to insulin, leading to elevated blood glucose levels. Insulin resistance exacerbates hyperandrogenism by stimulating the ovaries to produce more androgens. Additionally, high insulin levels suppress the production of sex hormone-binding globulin (SHBG) by the liver, a protein that regulates free androgen levels in the bloodstream (12,13). A decrease in SHBG results in higher levels of free androgens, worsening symptoms such as acne, hirsutism, and hair thinning. These metabolic abnormalities place women with PCOS at a higher risk for type 2 diabetes, cardiovascular disease, and other long-term health complications (12,13).

The disruption of follicular recruitment, selection, and ovulation in PCOS leads to irregular menstrual cycles and chronic anovulation. In a healthy menstrual cycle, multiple follicles are recruited at the beginning

of each cycle in response to FSH. These follicles grow and secrete estrogen, supporting endometrial development. Normally, one follicle becomes dominant, matures, and triggers an LH surge, leading to ovulation. The remaining follicles undergo atresia, a programmed cell death process. However, in PCOS, this natural progression is impaired. Due to insufficient FSH levels, multiple small follicles fail to mature and accumulate in the ovaries (13). The absence of a dominant follicle prevents the LH surge necessary for ovulation, resulting in chronic anovulation and infertility (13).

Due to irregular ovulation, progesterone levels remain low, contributing to further hormonal imbalances. As previously stated, progesterone plays a crucial role in maintaining the menstrual cycle and supporting pregnancy. In women with PCOS, the lack of ovulation means that the corpus luteum does not form, leading to persistently low progesterone levels. This deficiency results in irregular or absent menstrual periods and increases the risk of endometrial hyperplasia, a condition characterized by excessive growth of the uterine lining. Over time, prolonged anovulation and unopposed estrogen stimulation can increase the risk of developing endometrial cancer (12,13).

Pathophysiology of PCOS: The Role of Gonadotropin Dysregulation

Hyperandrogenism (elevated levels of male sex hormones) is a key feature in PCOS and plays a prominent role in the reproductive and metabolic dysfunction that is associated with the disorder. Elevated levels of androgens, particularly testosterone and dehydroepiandrosterone sulfate (DHEA-S),contribute to anovulation, irregular menstrual cycles, and dermatological symptoms such as pigmentation and rashes (14). Excess androgens are released primarily by ovarian theca cells, which become overactive to LH stimulation due to the de-regulation of HPG axis (14). Also, the peripheral conversion of androgens to estrogens further causes hormonal balance disruption, inflaming endocrine dysfunction in individuals with PCOS (14).

The overproduction of androgens in PCOS is primarily due to increased activity of cytochrome P450c17, a key enzyme involved with androgen biosynthesis within theca cells. Cytochrome P450c17 works in both the gonads and adrenal gland to regulate the body by synthesizing androgens such as testosterone precursors and other steroid hormones (15). Cytochrome P450c17 has two activities: the 17-hydroxylase activity and the 17,20-lyase activity. The17-hydroxylase activity is involved in the synthesis of cortisol in the adrenal

glands and sex steroids in the gonads (15). The 17,20-lyase activity, converts these precursor hormones to androgens (such as DHEA and androstenedione), which are essential for the synthesis of sex hormones like testosterone and estrogen (15).Cytochrome P450c17, only works when it is activated by hormones LH and adrenocorticotropic Hormone (ACTH). The human body regulates androgen production carefully, but in conditions like PCOS, the enzyme cytochrome P450c17 becomes overactive, causing hormonal imbalances (Figure 1) (15)

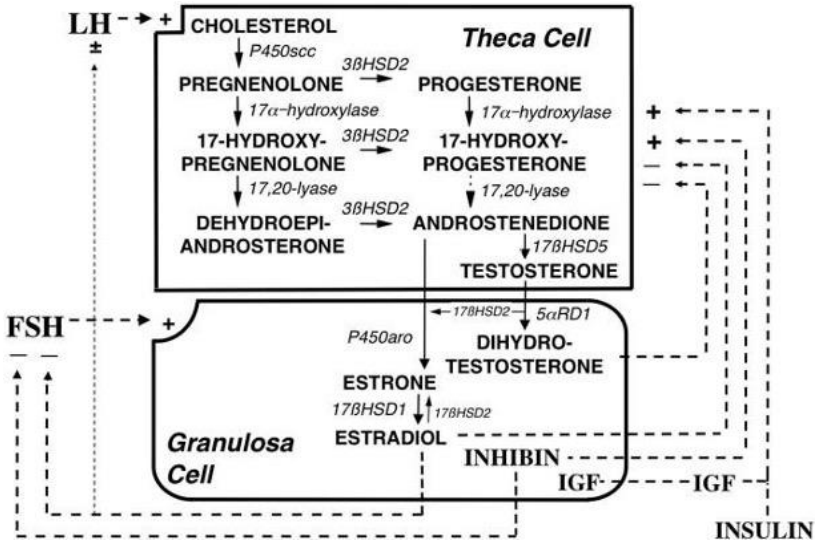

Figure 1-Regulation of the major steroid biosynthetic

Research has indicated that when theca cells get removed from women with PCOS through ovarian tissue biopsy or cell isolation procedures performed during surgery., there is an overactive response to LH stimulation, which results

in androgen levels continuously growing. The elevated production of androgens in PCOS is also due the adrenal glands hyperresponsiveness to ACTH stimulation which leads to an excess amount of DHEA-S production (14). In one study, researchers investigated whether adrenal androgen (AA) excess in PCOS is caused by an exaggerated response to ACTH and if this is due to a specific issue in hormone production (14). The study included 30 women that were separated into three groups: 1) 9 women with PCOS and excess AA, 2) women with PCOS without excess AA and 3) 12 were healthy controls. Participants underwent a 60-minute ACTH test, they were given a synthetic form of ACTH, usually through an intravenous (IV) injection, and their hormone levels were measured 30 and 60 minutes after injection (16). Results showed that women with PCOS and excess AA had significantly higher levels of DHEA and androstenedione compared to those without AA excess as their P values were greater than 0.05. They also had increased activity of the 17-hydroxylase enzyme, suggesting their adrenal glands produce more androgens than normal when stimulated by ACTH (16). This indicates that adrenal androgen excess in PCOS is linked to overactive hormone production in response to ACTH. However, the exact role that adrenal androgens play in PCOS is still under research (16).

In addition to ovarian androgen production, peripheral tissues, specifically adipose tissue, play an important role in hormonal dysfunction. Androgens such as testosterone and androstenedione undergoes a conversion process to become estrogen via the enzyme aromatase, which is highly expressed in adipose tissue (17). In normal menstrual cycles there are fluctuating estrogen levels, however women with PCOS often experience a weak estrogenic effect on the hypothalamus, specifically elevated estrogen levels. Elevated estrogen exposure can cause symptoms such as heavy menstruation, mood swings, breast cysts, and endometriosis (17). This disrupts the normal hypothalamic-pituitary feedback mechanisms, which prevents regular GnRH pulsatility from activating a surge in LH, which is a critical step in ovulation (10,17). This results in individuals with PCOS to continually experience anovulation, leading to oligomenorrhea to complete amenorrhea, which results in complete absence of menstrual cycles. Additionally, exposure to elevated estrogen can place an individual at a higher risk of endometrial hyperplasia, which is when the lining of the uterus becomes abnormally thick, if left untreated can progress to endometrial cancer, this shows the long-term effects of PCOS (10,17).Hyperandrogenism in PCOS can also lead to various dermatological symptoms, one of the most visible effects of being hirsutism, which can significantly impact self-esteem and the quality of life.

Between 70-80% of individuals with PCOS develop hirsutism (18). Hirsutism is defined as the excessive growth of dark, coarse hair in exposed skin surfaces such as the face, chest, and back. This condition arises because there is constant androgen stimulation of hair follicles, causing the hair follicles to transition from fine hairs to extremely pigmented hairs (18).

Hirsutism develops due to the fact that 5α-reductase, is the enzyme that converts testosterone to its more stronger form dihydrotestosterone (DHT), is overexpressed in the hair follicles of women with PCOS (19). Another common feature of hyperandrogenism is acne. Acne is caused by androgen stimulation of the sebaceous gland receptors which increases sebum production(oily substances), which can cause clogged pores and bacterial overgrowth. This is the perfect environment for the proliferation of cutibacterium acne, bacteria that can cause inflammatory acne lesions (18,20). PCOS- related acne often persists into adulthood and is harder to get rid of as it is more resistant to conventional treatments (18,20) Hyperandrogenism goes beyond the physical symptoms, it can cause psychological effects on the individual, such as anxiety and depression. These effects can impact one's self esteem, and overall mental well-being. (Figure 2) (18).

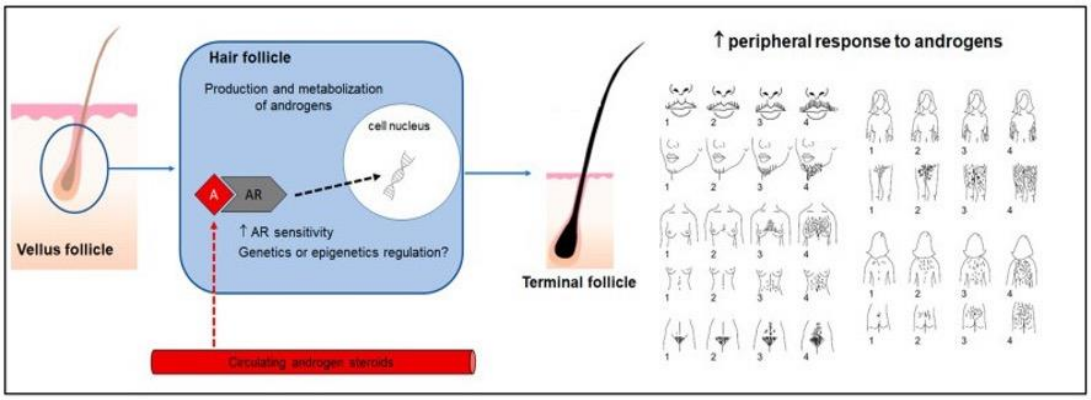

Figure 2-Effects the role of androgens on hair follicles and peripheral response (18).

Insulin Resistance and Type 2 Diabetes

PCOS is not just a reproductive disorder but also a metabolic disorder , with insulin resistance playing a pivotal role in its pathophysiology. Insulin resistance affects a large portion of women with PCOS, including those with a normal body weight, indicating that it is not just because of obesity but an innate feature of the disorder (21). Insulin resistance contributes to hyperinsulinemia (elevated levels of insulin in the bloodstream); which amplifies ovarian dysfunction by increasing androgen production, causing the disruption of normal follicular development, increasing the risk of type 2 diabetes and cardiovascular disease (21).Additionally, chronic inflammation, oxidative stress, and adipose tissue dysfunction also contribute to the worsening of hormonal imbalances and insulin resistance in PCOS.

Research has shown that insulin resistance in PCOS is caused by defects in post-receptor insulin signaling, specifically impaired phosphorylation of insulin receptor substrates (IRS-1 and IRS-2).This impairs insulin's ability to be able to

regulate glucose uptake and glycogen synthesis dwindles, while the ability to stimulate androgen production in the ovaries remains intact. In obesity-related insulin resistance, the excess fat presumably leads to insulin insensitivity (21). Insulin resistance is generally a tissue–specific issue, affecting various tissues in the body, and is not limited to PCOS. In PCOS, the skeletal muscle and adipose tissue have reduced glucose uptake, due to the weakened activation of the phosphoinositide 3-kinase (PI3K) signaling pathway, essential for insulin-mediated glucose transport (17,21).

However, insulin continues to stimulate androgen production in the ovaries, fueling hyperandrogenism while also impairing glucose metabolism. A consequence of hyperinsulinemia is insulin resistance, which worsens hormonal imbalances in PCOS. Insulin collaborates with LH to stimulate androgen synthesis by increasing the activity of cytochrome P450c17 (15,21). This leads to excess production of testosterone and androstenedione(a natural steroid), which further disrupts ovarian function (21,22). Additionally, insulin suppresses the hepatic production of sex hormone-binding globulin (SHBG), a glycoprotein responsible for binding androgens in the circulation. Lower SHBG results in increased free testosterone in circulation leading to heightened hirsutism, acne, and menstrual irregularities (21,22).This hormonal imbalance is a cycle where insulin resistance fuels hyperandrogenism, and hyperandrogenism which worsens metabolic dysfunction (Figure 3) (22).

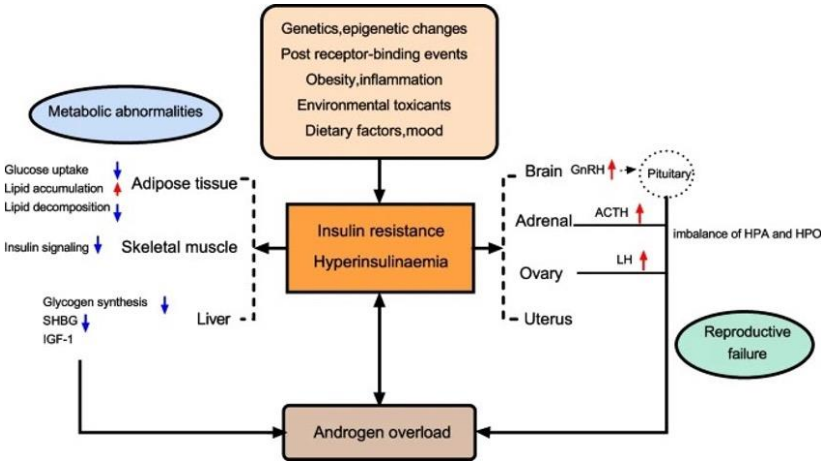

Figure 3- Summarizes the impact of insulin resistance, and hyperinsulinemia (22).

Due to chronic insulin resistance and hyperinsulinemia, women with PCOS are at a significantly higher risk of developing type 2 diabetes and metabolic syndrome .Studies show that women with PCOS are 4 times more likely to develop type 2 diabetes than those without the condition. Indeed, early signs of glucose intolerance in young adults and adolescents are frequently observed. Even in individuals with normal weight, impaired glucose tolerance and elevated fasting insulin levels are commonly observed (21). Additionally, the metabolic consequences of PCOS extend beyond diabetes risk, they have a significant effect on cardiovascular health. Women with PCOS frequently have dyslipidemia (abnormal levels of fat in the bloodstream), which can characterize by high triglyceride levels, low levels of high-density lipoprotein cholesterol, and increased levels of small lipoprotein particles—which are more likely contributing to atherosclerosis

(the built-up fats, cholesterol, and other substances in the artery walls).Furthermore, cholesterol imbalances, chronic inflammation and endothelial dysfunction further increase the risk of hypertension and cardiovascular disease(21,23).

There are also a high prevalence of metabolic syndrome in PCOS, which is a cluster of conditions which include, but are not limited to: central obesity, hypertension, and glucose intolerance. Studies suggest that up to 50% of individuals with PCOS meet the criteria for metabolic syndrome, reinforcing the strong link between reproductive and metabolic health in PCOS (24). Adipose tissue is not just for energy storage, it plays a crucial role in the metabolic dysfunction of PCOS, functioning as an endocrine organ that releases hormones and inflammatory cytokines. Individuals with PCOS often exhibiting abnormal adipokine levels such as: low adiponectin levels and elevated leptin levels, both of which contribute to insulin resistance (24,25). Adiponectin, is a hormone that improves insulin sensitivity, but decreases in individuals with PCOS, which leads to glucose intolerance and increased cardiovascular risk. Leptin is a hormone that is involved in regulating appetite and energy balance, is often elevated but becomes basically ineffective due to leptin resistance in PCOS, which further contributes to weight gain and metabolic imbalances (24,25).

Inflammation

Chronic low-grade inflammation is another key feature of PCOS. Women with PCOS show increased levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP).These inflammatory markers directly impair insulin signaling, causing it to further worsen insulin resistance and metabolic dysfunction (26).

Oxidative stress

Oxidative stress plays a major role in the progression of PCOS-related complications. Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses that contributes to endothelial dysfunction, which promotes atherosclerosis (buildup of fats) and cardiovascular complications (26). Additionally, high levels of oxidative stress have been shown to negatively affect ovarian function, impairing follicular development and hormone regulation, further complicating fertility outcomes. n, which promotes atherosclerosis (buildup of fats) and cardiovascular complications (26).

Genetics

PCOS is not just influenced by reproductive and metabolic factors, it is an intricate disorder that is also influenced by both genetic and environmental factors. While scientists have yet to determine a cause, there is strong evidence suggesting that PCOS runs in families, meaning that it could

be heritable, with multiple generations often affected. Studies using genome-wide association studies have identified several key genes that are involved in hormonal regulation, insulin signaling, and ovarian development.

However, genetic inheritance alone does not fully explain why PCOS develops or why it presents differently in individuals. There has been recent research that has highlighted epigenetic modifications such as DNA methylation and histone modifications —chemical changes to DNA that regulate gene expression without altering their sequence, which is a critical factor in PCOS development (27). It is important to note that maternal health during pregnancy may have a direct influence on fetal development in ways that can increase the risk of PCOS later in life. Understanding how genetics, epigenetics, and early-life factors contribute to PCOS may lead to more personalized and effective treatment approaches in the future. There have been several genes that are associated with hormone regulation, ovarian development, and metabolism that have been identified as major contributors to PCOS. Some of the most studied genes are: follicle-stimulating hormone receptor(FSHR), luteinizing hormone/choriogonadotropin receptor (LHCGR), insulin receptor(INSR), anti-Müllerian hormone (AMH),each gene plays a distinct role in PCOS complex pathology (27,28).

FSHR gene controls how the body responds to FSH, which is crucial for egg development and ovulation. Variants in FSHR can reduce ovarian sensitivity to FSH, making it harder for eggs to mature and increasing the

likelihood of anovulation in people with PCOS (27,28). The LHCGR gene encodes the receptor for LH, which stimulates the ovaries to produce androgens. Elevated LH levels are a hallmark of PCOS, and specific LHCGR variants may contribute to excess androgen production, causing symptoms such as irregular periods and hirsutism to worsen. One of the most consistent key disturbances in PCOS is insulin resistance (27,28). The INSR gene has an important role in glucose metabolism since it encodes the insulin receptor, which mediates glucose uptake in target tissues such as muscle and adipose tissue. Research has shown that mutations in the INSR genes play a crucial role in insulin signaling, making it more difficult for cells to absorb glucose properly (27,28).Insulin resistance leads to hyperinsulinemia which in turn stimulates the ovaries to produce more androgens, further disrupting reproductive function (27,28). Finally, the AMH gene codes for the anti-Müllerian hormone (AMH) which is a significant factor in PCOS as it is an important regulator of follicular growth and ovarian function. Women with PCOS often have higher-than-normal AMH levels, which may contribute to excessive follicular arrest, which is when eggs fail to mature properly, leading to anovulation (27,28). Certain genetic variants in the AMH gene and its receptor AMHR2 are thought to increase ovarian sensitivity to AMH, which further impaired the egg development and contributes to PCOS symptoms. While genetics plays a crucial role in PCOS, other factors including, epigenetic factors and environmental influences also shape how

the disorder presents in different individuals.

Epigenetics

Epigenetics refers to modifications in gene expression that do not involve changes in the DNA sequence but instead, regulate gene activity such as DNA methylation, histone modifications, and non-coding RNAs (27). While genetic mutations are established at birth, epigenetic modifications are able to change gene expression over time (27). These modifications can be influenced by hormonal fluctuations, diet, stress, and environmental exposures, which can explain why PCOS symptoms present differently in individuals with similar genetic backgrounds. DNA methylation, which is a process where methyl groups are attached to the cytosine bases in DNA and suppress gene expression. Abnormal DNA methylation has been found in key genes associated with PCOS. Studies have shown that excess methylation of the FSHR gene for example, can reduce its expression, making ovarian follicles less responsive to FSH, which contributes to irregular ovulation (27).

Additionally, altered methylation patterns in INSR and LHCGR genes have been linked to higher insulin resistance and excessive androgen production, two major hallmarks of PCOS (27,28).Histones are proteins that help package DNA into the chromatin. When histones undergo modifications such as acetylation or methylation, they can affect the

accessibility of genes by changing how tightly the DNA is wound. These modifications influence whether certain genes are “turned on” or “turned off.” In PCOS**,** histone modifications in androgen-related genes like cytochrome P450c17 have been linked to increasing testosterone production, which fuels symptoms such as hirsutism and acne (15,28). These findings suggest that epigenetic dysregulation may reinforce the hormonal imbalances seen in PCOS over time.

MicroRNAs

Non-coding RNAs, particularly microRNAs (miRNAs), regulate gene activity. Researchers have found that specific miRNAs, such as miR-93 and miR-223, are altered in PCOS, and have been found to interfere with insulin signaling and increasing inflammation (29). This could provide an explanation on why chronic low-grade inflammation is so common in individuals with PCOS and why it contributes to metabolic complications (29).

Maternal-Fetal Programming and Transgenerational Risk

Emerging evidence suggests that PCOS risk may be determined in utero through maternal-fetal programming, a process in which the environment in the womb such as exposure to high androgen or insulin levels may affect the fetal development and predisposes offspring to metabolic and reproductive

disorders, that can cause PCOS more likely to be develop later in life(29).

To examine maternal-fetal programing, animal studies show that fetal exposure to excess androgens can lead to disruptions in ovulation, insulin resistance, and hormone imbalances similar to those seen in PCOS (29). Pregnant mice were given dihydrotestosterone (DHT), a potent androgen, to replicate the elevated androgen levels observed during pregnancy. The study revealed that the female offspring exhibited hormonal abnormalities typical of PCOS, including raised levels of testosterone and LH (29).These offspring also displayed irregular estrous cycles, mirroring the menstrual irregularities and anovulation seen in women with PCOS. Additionally, the offspring developed insulin resistance, a defining characteristic of PCOS that contributes to metabolic complications like obesity and a higher risk of type 2 diabetes. The findings of this study showed the significant role prenatal androgen exposure plays in the development of both metabolic dysfunction and reproductive irregularities associated with PCOS(29). This research provides compelling evidence that exposure to androgens early in life can predispose offspring to symptoms resembling PCOS, emphasizing the importance of maternal health and its long-term impact on the development of the condition. Furthermore, this study supports the concept of transgenerational inheritance of PCOS risk, suggesting that maternal health, particularly regarding androgen exposure, could increase the likelihood of PCOS manifesting in subsequent generations (29).

Additionally, human studies suggest that daughters of women with PCOS are more likely to develop the condition themselves, supporting the idea of transgenerational inheritance of PCOS risk. A study was conducted to explore this idea, in the study there were a total of 183 women, 99 of which were daughters of women with PCOS and 84 daughters of women without PCOS which was the control group. The researchers conducted glucose tolerance tests, hormone stimulation tests, and ovarian ultrasounds to assess their metabolic and reproductive function(30). The results showed that, at all stages of puberty, the daughters whose mothers had PCOS, had larger ovarian volumes and higher insulin levels than the control group. By the later stages of puberty , they also had higher levels of testosterone, LH, and 17-hydroxyprogesterone, indicating hormonal imbalances commonly seen in PCOS(30).Given the early onset of these issues, daughters of women with PCOS are at a significantly higher risk for developing both metabolic and reproductive complications later in life. It is also noted that Women with PCOS are more likely to develop gestational diabetes, which can expose the fetus to high blood sugar levels. This may increase the child's risk of developing insulin resistance, obesity, and metabolic syndrome later in life. Some researchers believe that epigenetic changes associated with PCOS, such as DNA methylation in metabolic and reproductive genes, may be passed from mother to child, further increasing the likelihood of developing PCOS (30).

CHAPTER 3: DIAGNOSTIC CRITERIA AND BIOMARKERS OF PCOS

Diagnosing PCOS correctly and at the right time is still a challenge due to the wide range of symptoms, different presentations, and always evolving diagnostic standards. Over the years, multiple different medical organizations have developed their own criteria, each focusing on different aspects of the condition. The three most used diagnostic frameworks are the: Rotterdam Criteria, the National Institutes of Health (NIH) Criteria, and the Androgen Excess & PCOS Society (AE-PCOS) Criteria (4,29,31). In addition to clinical evaluation, biochemical markers, such as hormonal imbalances such as the LH/FSH ratio and anti-Müllerian hormone (AMH) levels, help confirm a diagnosis. Ultrasound imaging is also widely used to assess ovarian morphology, as they provide further confirmation of the disorder . However, to reiterate that PCOS is more than just a hormonal disorder; it also affects mental health such as, self-esteem. A comprehensive approach that considers both physical and emotional well-being is key to improving diagnosis and management (4,29,31).

Since PCOS symptoms vary widely, different diagnostic guidelines focus on different aspects of the disorder. First is the Rotterdam Criteria, Developed in 2003 by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, the Rotterdam Criteria as previously mentioned defines PCOS as having at least two of the following three features (4,29,31): a) irregular ovulation or anovulation, which leads to inconsistent or absent menstrual cycles, b) clinical and/or biochemical signs of

Hyperandrogenism, meaning excess male hormones either clinically such as acne, or biochemically through blood tests, c.) polycystic ovarian morphology on using ultrasound where it should show that each ovary has to have at least 12 small follicles, and the size of the ovary has to be larger 10 milliliters.

Because only two out of three criteria are needed for diagnosis, the Rotterdam Criteria captures a wider range of PCOS cases, including milder forms. However, some scientists argue that because there is such a wide range of cases, it may lead to individuals who have mild ovarian irregularities may be over diagnosed even though they do not exhibit the classic metabolic and hormonal imbalances of PCOS(29,31). The National Institutes of Health (NIH) Criteria, established in 1990 was the first formal guidelines created for diagnosing PCOS (29). They define PCOS as having hyperandrogenism or chronic anovulation (persistent irregular menstrual cycles).Unlike the Rotterdam Criteria, the NIH Criteria does not require the presence of polycystic ovarian morphology for diagnosis (29,31).As a result, it excludes milder cases and focuses on the more severe metabolic and hormonal aspects of PCOS. This can lead to individuals with PCOS getting underdiagnosed and not being able to receive the proper treatment (29,31). The Androgen Excess & PCOS Society Criteria was created in 2006,emphasizes that PCOS is primarily an androgen-excess disorder. It defines PCOS as: hyperandrogenism which is required for diagnosis, and ovarian dysfunction either in the form of irregular ovulation or polycystic ovarian morphology (29,31).Since hyperandrogenism is mandatory under these criteria,

this definition excludes non-hyperandrogenic PCOS cases recognized under the Rotterdam Criteria , making it more specific but less inclusive. The variability between these three diagnostic criteria's have led to four recognized PCOS phenotypes, ranging from severe to mild: The four classification of the PCOS phenotypes (29,31,32): a) Classic PCOS (Phenotype A) – Hyperandrogenism + anovulation + polycystic ovaries, b) Metabolic PCOS (Phenotype B) – Hyperandrogenism + anovulation (without polycystic ovaries), c) Ovulatory PCOS (Phenotype C) – Hyperandrogenism + polycystic ovaries (but with normal ovulation), d) Mild PCOS (Phenotype D) – Anovulation + polycystic ovaries (without hyperandrogenism). Classic PCOS (Phenotype A) is the most severe form and is associated with higher metabolic risks such as insulin resistance, obesity, and cardiovascular disease. By contrast, Mild PCOS (Phenotype D) is less severe and mainly affects fertility rather than metabolism. The inconsistency in the diagnostic guidelines and the lack of a universal definition continues to create inconsistencies in prevalence rates, research findings, and treatment approaches (31,32).

Since PCOS presents with a variety of endocrine and ovarian abnormalities, blood tests and imaging techniques help confirm a diagnosis. LH/FSH Ratio used as a diagnostic marker a common but inconsistent marker. One of the earliest recognized hormonal imbalances in PCOS was an elevated LH/FSH ratio. Normally FSH are secreted in a balanced pattern to be able to regulate ovulation. However, in PCOS, GnRH pulsatility

increases, which causes LH secretion to increase, leading to an LH/FSH ratio greater than 2:1 (10,11,27,31,32,33). This hypersecretion of LH stimulates ovarian theca cells which results in excessive androgen production, contributing to symptoms like balding and difficulty conceiving (31,32). However, not all individuals with PCOS show this imbalance, making it an unreliable standalone diagnostic tool (31,32). Another diagnostic marker is Anti-Müllerian Hormone (AMH). AMH is produced by granulosa cells during the early stages of follicles and reflects the number of immature eggs in the ovaries. Since PCOS is characterized by an excess amount of small follicles, AMH levels are often 2-3 times higher than normal, due to follicular arrest. Because AMH can be measured through a simple blood test, it is gaining popularity as a non-invasive biomarker for PCOS (10,11,27,31,32,33). However, there is no universally agreed-upon cutoff value, and AMH levels naturally decline with age, limiting its usefulness in older patients (32,33). Ultrasound imaging plays a crucial role in assessing polycystic ovarian morphology. The key features that PCOS exhibit include: a) each ovary has to have at least 12 small follicles, b)the size of the ovary has to be larger 10 milliliters, c) a distinct "string of pearls" appearance, small follicles lining the ovarian edge. However, not all women with polycystic ovaries have PCOS, and ovarian morphology alone is not enough for diagnosis as they can be seen in healthy women. Additionally, transvaginal ultrasound is not routinely performed in adolescents, making

hormonal markers more relevant for younger patients(10,11,27,31,32,33) .

CHAPTER 4: CURRENT AND EMERGING TREATMENT STRATEGIES

Polycystic ovary syndrome (PCOS) is a complex condition that affects multiple aspects of health, including reproductive, metabolic, and dermatological well-being. Because the symptoms and severity of PCOS vary from person to person, treatments must be tailored to address specific concerns such as hormonal imbalance, insulin resistance, menstrual irregularities, hyperandrogenic symptoms, and fertility challenges. Managing PCOS typically involves a combination of medications, lifestyle modifications, and, in some cases, surgical procedures. While traditional treatments such as birth control pills and insulin-sensitizing drugs remain the standard approach, newer therapies, including targeted hormone treatments and regenerative medicine, are emerging as potential breakthroughs (34).

Women with PCOS who are not trying to get pregnant are treated with combined oral contraceptives which are often the first type of treatment. These birth control pills contain a combination of estrogen and progestin, which help to regulate menstrual cycles by suppressing gonadotropin secretion and stabilizing hormone levels. This treatment also reduces excess androgens by increasing levels of sex hormone-binding globulin (SHBG), a protein that binds to and inactivates free testosterone (34). These birth

controls also improve acne and reduce excessive hair growth by reducing the effect of androgens on the skin and hair follicles (34).The most effective type of combined oral contraceptives for PCOS contain low-dose ethinyl estradiol that are combined with progestins that have anti-androgenic properties, such as drospirenone, cyproterone acetate, or dienogest (34). These progestins block androgen receptors and reduce androgen synthesis. However, combined oral contraceptives are not suitable for all women, as they may increase the risk of blood clots, weight gain, or mood changes, particularly in those with obesity or a history of cardiovascular disease (34).

Since many women with PCOS have insulin resistance, there are medications that improve insulin sensitivity that can help manage symptoms. Insulin-sensitizing agents such as Metformin and Thiazolidinediones play a crucial role in treatment. Metformin helps reduce hepatic glucose production and increases peripheral insulin sensitivity. By suppressing gluconeogenesis and enhances insulin sensitivity by activating AMPK, which improves glucose uptake and utilization in peripheral tissues (35). Metformin is a commonly prescribed drug for type 2 diabetes, which helps lower blood sugar and insulin levels, which in turn reduces androgen production and improves menstrual regularity. Many women with PCOS also experience modest weight loss when taking metformin (35). Studies suggest that taking metformin by itself or combining it with lifestyle changes can restore ovulation in women with PCOS (35). However, it is the least effective

fertility medication in comparison to others such as clomiphene citrate as discussed below.

The other insulin-sensitizing agent ,Thiazolidinediones such as pioglitazone, work by improving insulin sensitivity in fat and muscle cells by activating PPAR-γ receptors in adipose tissue. They activate these receptors by binding to them and forming a heterodimer with retinoid X receptor (RXR), and then binding to specific DNA sequences (PPREs) to increase transcription of target genes involved in carbohydrate and lipid metabolism (35). However, thiazolidinediones medications are used less frequently because they can cause weight gain and fluid retention.

For women with PCOS who want to get pregnant, there are medications that induce ovulation that can improve their chances of getting pregnant. These include clomiphene citrate and letrozole. Clomiphene citrate is a widely used treatment that stimulates the ovaries to release eggs in women who do not produce eggs but still want to get pregnant (36). It is a selective estrogen receptor modulator that blocks estrogen receptors in the hypothalamus, leading to increased FSH secretion and follicular development (36).However, it can increase the risk of multiple pregnancies and may negatively affect the uterine lining, reducing the chances of implantation being successful (36).

Letrozole is commonly used to treat certain types of breast cancer in women who have already stopped menstruating. It is also an aromatase

inhibitor which is basically a class of medications that block the enzyme aromatase, which converts androgens into estrogen (36). It works by inhibiting estrogen synthesis, leading to greater FSH stimulation with better endometrial effects, such as improving endometrial thickness, leading to higher pregnancy rates (36).Letrozole has been shown to be more effective than clomiphene citrate for ovulation induction. There have been recent studies that confirm that letrozole achieves higher ovulation and live birth rates than clomiphene citrate (36).

Excess androgens in PCOS can lead to unwanted symptoms such as acne, skin tags in armpits or neck, and balding. Anti-androgen medications help block the effects of these hormones. Anti-androgen medications include Spironolactone, Finasteride, and Flutamide. Spironolactone is commonly used in combination with other medicines to treat hypertension (high blood pressure) and heart failure. It can increase urine output without causing potassium loss in the urine (37). In terms of hyperandrogenism spironolactone is a diuretic with anti-androgenic properties, it inhibits 5α-reductase and blocks androgen receptors, reducing excessive hair growth and acne. Flutamide is another strong androgen receptor antagonist, however it is rarely prescribed due to its potential for liver toxicity (37). Finasteride is also a 5α-reductase inhibitor that reduces dihydrotestosterone levels by blocking the production of male hormones that stop hair growth , so taking this medication improves hair growth and reduces baldness in PCOS (37).Since

these medications can cause birth defects, they should always be taken with reliable contraception if pregnancy is not desired (37).

For women who do not respond to fertility medications, an alternative option is available, namely, laparoscopic ovarian drilling which is a minimally invasive surgical procedure that can help restore ovulation(38).During the procedure, a surgeon uses a laser or small electrical needle to create tiny holes in the ovarian surface, reducing the overproduction of androgens and stimulating ovulation (38). There are pros and cons to this treatment. While the procedure can restore ovulation in up to 80% of women, and lower risk of multiple pregnancies compared to fertility drugs, it can cause ovarian damage or scarring. Further, the procedure lacks long-term benefits, as hormone levels can return to pre-surgical levels over time (38).While laparoscopic ovarian drilling is an option for women who have not had success with pharmacological therapies, it is generally considered a last resort due to the potential risks.

Since obesity and insulin resistance can worsen PCOS symptoms, lifestyle changes play a fundamental role in the management of the symptoms. Certain diets have been shown to helpimprove PCOS symptoms by regulating blood sugar levels, reducing insulin resistance, and lowering inflammation. The first diet is the Ketogenic diet , which is a low-carb, high-fat diet that significantly lowers insulin levels and promotes fat loss (39). Examples of the type of food eaten under this are: fish, meat, and non-starchy

vegetables like broccoli and zucchini (39). Another diet that can be helpful is the Mediterranean diet. This diet is rich in healthy fats, fiber, and antioxidants, which help regulate metabolism and improve fertility. Examples of the type of food eaten under this diet are: whole grains, vegetables, nuts, and seafood. Finally, the Low-glycemic index diet helps stabilize blood sugar and reduce insulin spikes, minimizing androgen excess (39).Examples of the type of food to eat under this diet are: fruit, eggs, and grain (Figure 4) (39).

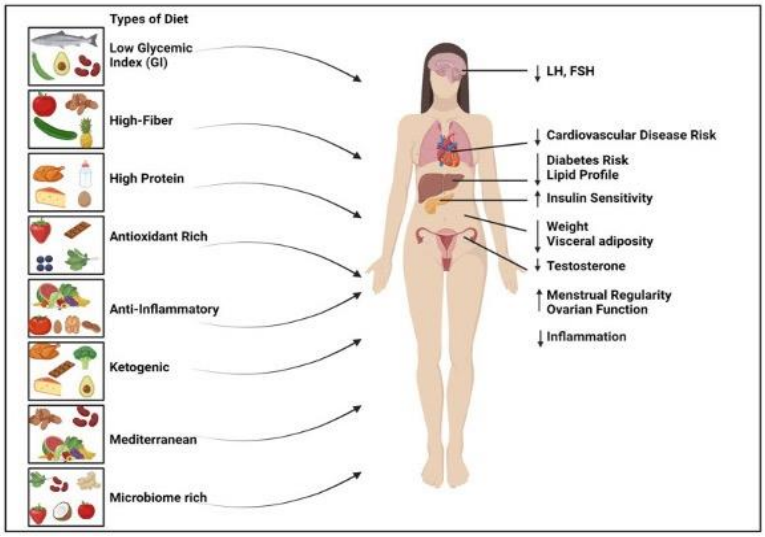

Figure 4- Depicts the effects different dietary patterns have on reducing PCOS (39).

Regular physical activity can also help regulate hormones, improve insulin sensitivity, and promote weight loss in women with PCOS. Some exercises that may help are aerobic exercises, such as walking, swimming, or cycling, which improves cardiovascular health and reduces body fat. Another one is strength training , which helps lower testosterone levels and

improves lean muscle mass (39). Finally, women with PCOS can do high-intensity interval training commonly known as HIIT training, which has been shown to be particularly effective in reducing visceral fat and inflammation (39). Many women with PCOS often turn to natural supplements to help manage their symptoms. Some natural supplements are inositols, specifically Myo- and D-Chiro Inositol, which improve insulin sensitivity and restore ovulation (39). Another common natural supplement is Vitamin D; deficiency in vitamin D is very common in PCOS, so taking a supplement may improve insulin resistance and reduce inflammation (39). Another supplement is omega-3 fatty acids, which can help reduce testosterone levels and improve lipid profiles. Finally taking probiotic supplements significantly supports gut health, which is increasingly recognized as playing a role in PCOS (39).

CHAPTER 5: CUTTING-EDGE RESEARCH TOWARD A CURE

PCOS remains one of the most complex and challenging endocrine disorders to treat. Current therapies primarily focus on managing symptoms rather than addressing the root cause, but emerging research is shifting toward finding long-term solutions and potential cures. Scientists are exploring innovative approaches such as stem cell therapy, gene editing, kisspeptin therapy, and microbiome-based treatments, each offering new hope for women living with PCOS. While these treatments are still in the early stages of development, they have the potential to revolutionize the way PCOS is managed in the future.

Stem cell therapy

Stem cell therapy has gained traction in reproductive medicine as a promising new way to restore ovarian function. Stem cells are very unique because they have the ability to develop into different types of cells and repair damaged tissues. When needed, they can also make copies of themselves(40). In terms of treating infertility, stem cells can be used in two main ways either through direct transplantation or in vitro differentiation. Direct transplantation is when stem cells or the substances they release such as paracrine factors can be introduced into reproductive organs to promote healing or regeneration (40). In vitro differentiation is when stem cells can be grown and transformed into germ cells or gametes (egg or sperm cells) in a lab setting (40).Paracrine

factors play a key role in these processes by encouraging nearby cells to mature into specialized cell types, regulating inflammation and repair in surrounding tissues, and influencing the behavior of other stem cells produced, such as mesenchymal stem cells. These factors are what allows for communication between stem cells and more developed cells (40).Because PCOS is characterized by ovarian dysfunction, disrupted follicle development, and hormonal imbalances, researchers believe that stem cells could repair damaged ovarian tissue and restore normal reproductive function(40).

Recent studies suggest that adult ovarian stem cells have the ability to regenerate follicles, providing a potential solution for women struggling with anovulation and reduced ovarian reserve. Unlike traditional fertility treatments that stimulate existing follicles, ovarian stem cells can help create new ones, offering a more sustainable approach to fertility restoration (40). The two main types of ovarian stem cells are very small embryonic-like stem cells , which are tiny and difficult to find, and larger ovarian stem cells, which can be seen more easily by scraping the surface of the ovary and examining the sample (40). Scientists have successfully isolated and cultured ovarian stem cells, demonstrating their ability to develop into egg-like cells. In lab experiments, transplanting these stem cells into dysfunctional ovaries has led to restored hormone production and ovulation. While this research is still in its early phases, ongoing clinical trials are assessing the safety and

effectiveness of this approach in humans. Also, another type of stem cell found in human ovaries, known as germ stem cells, can be isolated and grown in a lab, and potentially lead to the formation of new eggs (40).

Another promising area of research focuses on mesenchymal stem cells (MSCs)**,** which have powerful anti-inflammatory and hormone-regulating properties. These cells are unique because of their ability to attach to surfaces and transform into different types of cells, including bone, fat, and cartilage cells. Mesenchymal stem cells**,** derived from bone marrow, fat tissue, or umbilical cord blood have shown the ability to reduce ovarian fibrosis, a condition that prevents follicles from developing properly. They also can restore normal estrogen and progesterone levels, leading to regular menstrual cycles (40). Additionally, they can regulate androgen production, reducing symptoms like acne and excess hair growth.

Some types of commonly used Mesenchymal stem cells are bone marrow and umbilical cord. Bone marrow MSCs are cells that have shown to improve the thickness of the uterine lining and increase estrogen receptors, which may help fertility. Umbilical Cord MSCs (UC-MSCs) ,are easily collected and carry a low risk of immune rejection (40). These cells can support ovarian function, reduce inflammation, and enhance fertility. Studies in animals have shown promising results. For example, in 2017, researchers

observed that when umbilical cord MSCs were transplanted into rats, that their ovarian function improved: there were more follicles present, levels of FSH decreased, levels of anti-Müllerian hormone (AMH) and estrogen increased, suggesting improved ovarian reserve (40).

The use of autologous stem cells, which are stem cells taken from a person's own body, is generally considered safer, more ethical, and less likely to cause immune rejection. Therefore, they hold significant potential for future medical treatments. However, the use of embryonic stem cells raises ethical and legal concerns because it involves the destruction of human embryos (40). The debate around this often depends on how different societies and legal systems define the moral and legal status of an embryo. In contrast, induced pluripotent stem cells (iPSCs) and adult stem cells are not connected to embryos, making them less controversial and more widely accepted (40).Moving forward, researchers are working on ways to refine stem cell treatments, making them safer and more effective for long-term use.

Gene therapy

Since PCOS has a strong genetic component, scientists are exploring gene editing technologies like CRISPR-Cas9 to correct genetic mutations associated with the disorder. While gene therapy is still relatively new, it still presents an exciting possibility for a permanent solution to PCOS by targeting its underlying

genetic causes. One of the biggest defining features of hormonal imbalances in PCOS is excess LH, which leads to increased androgen production and ovulation problems. Researchers are investigating how gene editing could modify the luteinizing hormone receptor gene through either gene silencing or CRISPR editing, helping to restore normal hormone levels and improve ovulation (41).CRISPR–Cas9 is an innovative genetic tool that allows scientists to make precise changes to DNA. This technique is inspired by a natural defense system found in bacteria, which helps them fight off viruses. CRISPR part is a system that bacteria use to recognize and defend against viruses by storing small pieces of viral DNA. Cas9 is an enzyme that acts like molecular scissors, cutting DNA at specific locations (41) By using RNA to direct Cas9 to a precise spot in the DNA, scientists can add, remove**,** or modify genes with remarkable accuracy. As previously stated, PCOS is linked to overactive androgen production due to increased activity of certain genes, such as CYP17A1 and SRD5A2. CYP17A regulates 17α-hydroxylase activity, regulates androgens. SRD5A2 converts testosterone to dihydrotestosterone (41). By editing these genes, scientists hope to reduce excess testosterone levels, which could improve symptoms like acne, excessive hair growth, and infertility. Beyond CRISPR, RNA interference (RNAi) therapy represents an alternative approach, which works by "turning off" overactive genes (41,42). RNAi are being explored to silence overactive genes

linked to PCOS pathology. Studies suggest that using RNAi to modify the insulin receptor gene could help reduce insulin resistance, a key driver of PCOS symptoms. While gene therapy is still experimental, there is hope that in the future, it could offer a one-time treatment to correct PCOS at a molecular level (41,42).

Kisspeptin therapy

One of the most significant breakthroughs in PCOS research is kisspeptin therapy, which focuses on correcting hormonal imbalances at their source. Kisspeptin is a key hormone that helps control reproductive function. It is a neuropeptide that is encoded by the KISS1 gene, and plays a critical role in stimulating the release of GnRH, which regulates LH and FSH levels (42,43). Kisspeptin is produced by two types of brain cells, kisspeptin neurons and KNDy neurons. These neurons release kisspeptin, which then binds to receptors on GnRH neurons. This interaction is what can trigger the release of GnRH, which in turn stimulates the production of LH and FSH. In PCOS, kisspeptin is overproduced, which over activates the reproductive hormone system also known as the HPG axis. This leads to an increased LH/FSH ratio, excess androgen production and irregular ovarian function (42,43). Kisspeptin therapy is carefully controlled, meaning it delivers the hormone at specific doses and in a regulated manner to help restore normal hormone patterns. The real issue in PCOS isn't just

high kisspeptin levels, but rather that GnRH pulses are too fast and unbalanced, leading to too much LH and not enough FSH ,which is needed for proper follicle development (43).Kisspeptin therapy works by restoring the proper timing and rhythm of GnRH pulses, helping to balance LH and FSH production**.** This can lead to more regular ovulation and better hormone regulation. Many women with PCOS struggle to ovulate regularly even with medications like clomiphene citrate or letrozole. Kisspeptin therapy provides a more natural way to stimulate ovulation without overstimulating the ovaries the way traditional fertility drugs do. It also presents a safer alternative for women undergoing assisted reproduction such as IVF, reducing the risk of ovarian hyperstimulation syndrome**,** a common complication of fertility treatments. Because kisspeptin therapy targets the root of hormonal dysregulation, it could potentially serve as a long-term alternative (Figure 5) (43) . Early studies show promise, but further research is needed to fully understand how kisspeptin could be used in PCOS treatment

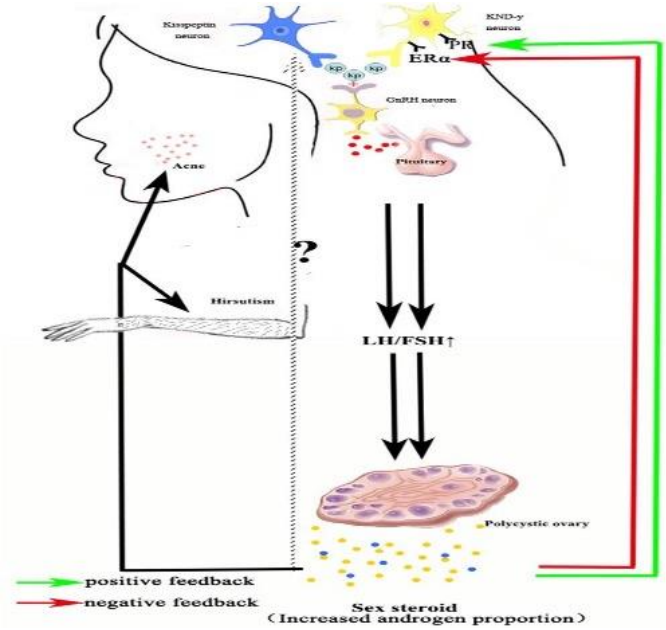

Figure 5- Kisspeptin involvement in PCOS (43).

Targeting Gut Microbiome

A growing body of research suggests that gut bacteria play a key role in PCOS, influencing metabolism, inflammation, and hormone regulation(44). Women with PCOS often have imbalances in gut bacteria, which may contribute to insulin resistance, androgen excess, and chronic inflammation. There is a theory called Dysbiosis of Gut Microbiota in PCOS (DOGMA) that explains how an unhealthy gut might contribute to PCOS. According to this theory discusses how diets high in sugar and unhealthy fats and low in fiber can disrupt the balance of gut bacteria, weakening the protective lining of the intestine (44).When the gut lining becomes too permeable it can cause a leaky gut which allows, harmful substances like

lipopolysaccharides to enter the bloodstream. Lipopolysaccharides can trigger the immune system, leading to chronic inflammation and interfering with insulin function, causing insulin resistance (44). Gut bacteria influence insulin production and androgen, both of which are key factors in Postwomen with PCOS often have different gut bacteria compared to those without the condition, and certain gut bacteria imbalances may be linked to higher testosterone levels and menstrual irregularities. Changes in gut health can trigger chronic inflammation, making PCOS symptoms worse. The gut and brain communicate through the gut-brain axis, which may play a role in hormonal imbalances in PCOS (44). Gut bacteria produce various metabolites such as short-chain fatty acids and bile acids that influence HPG axis, ovarian function, metabolism, and insulin sensitivity (44).

Recent research has found that bile acids, which help digest fats, may also play a role in ovarian health and hormone balance**.** Women with PCOS have been shown to have higher levels of certain bile acids in their ovarian fluid, suggesting a link between gut health, bile metabolism, and reproductive function (44). Recent research suggests that probiotics and prebiotics, which help restore a healthy balance of gut bacteria, may have significant benefits for PCOS. Clinical studies indicate that probiotic supplementation can improve insulin sensitivity, reduce testosterone levels, and help regulate menstrual cycles. Future research is exploring whether specific probiotic strains could be used as a targeted treatment for PCOS,

potentially offering a non-invasive and natural way to manage symptoms.

CONCLUSIONS AND FUTURE DIRECTIONS

In this thesis, we have thoroughly examined the role of gonadotropin dysregulation in the pathophysiology of Polycystic Ovary Syndrome (PCOS) and how it contributes to the reproductive, metabolic, and hormonal dysfunctions observed in affected individuals. Our exploration of the hypothalamic-pituitary-gonadal (HPG) axis and its dysregulation in PCOS has highlighted how abnormal GnRH pulsatility leads to the elevated LH/FSH ratio, excessive androgen production, and anovulation, which are core features of the disorder. These disruptions not only impair reproductive health, leading to infertility and menstrual irregularities, but also contribute to metabolic dysfunctions, such as insulin resistance and hyperandrogenism. The clinical manifestations of PCOS, such as hirsutism, acne, and irregular periods, are directly linked to this underlying hormonal imbalance. Furthermore, the association between PCOS and metabolic syndromes, including obesity, type 2 diabetes, and cardiovascular disease, underscores the complexity of the disorder and the need for comprehensive approaches to treatment.

Insulin resistance further worsens both metabolic and reproductive outcomes, increasing the risk of type 2 diabetes and cardiovascular disease. While genetics play a role, epigenetic and environmental factors influence disease severity and progression. Effective management requires a holistic approach, combining medical treatments, lifestyle modifications, and mental health support. While traditional therapies like birth control and metformin remain key, emerging

treatments such as targeted hormone therapy, regenerative medicine, and microbiome-based interventions offer new hope. Advances in stem cell therapy, gene editing, and personalized medicine may one day shift PCOS treatment from symptom management to a true cure.

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