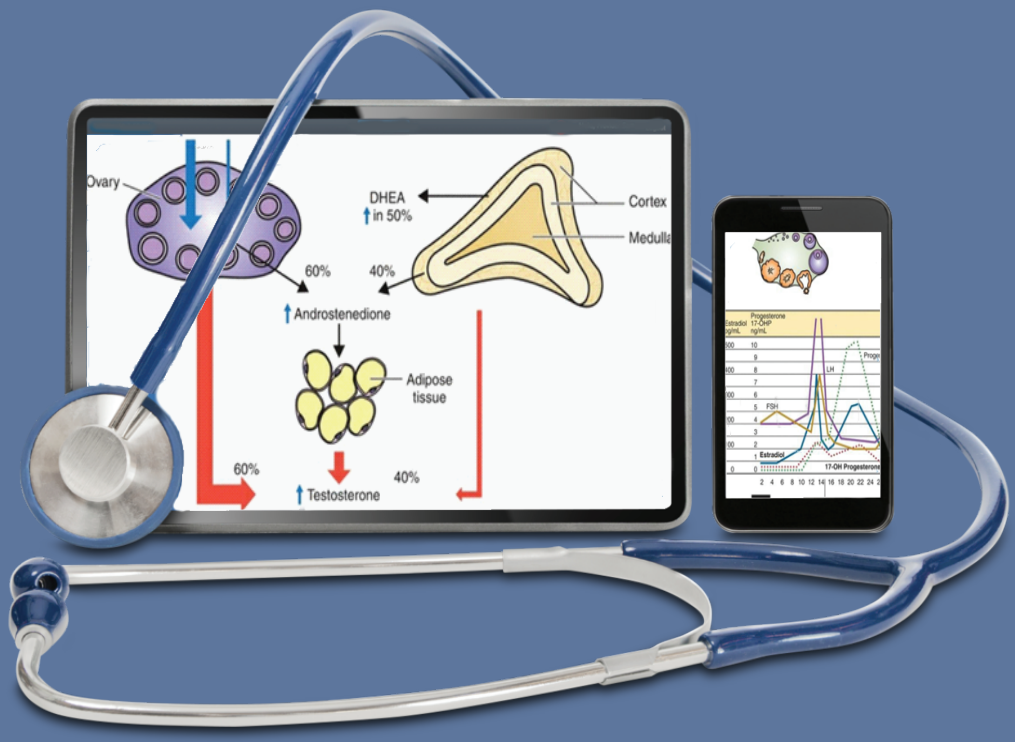
COMPREHENSIVE OVERVIEW OF PCOS DISEASE



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PREFACE

Academicians,

This book aims to provide a scientific review on polycystic ovary syndrome (PCOS). PCOS is a syndrome that has significant impacts on female reproductive health and affects many women globally. This book targets to present a comprehensive scientific perspective on the etiology, pathophysiology, diagnostic methods, treatment options, and recent research findings of PCOS.

The complexity of PCOS and its diverse symptoms underscore the need for a deeper understanding of this syndrome and emphasize the necessity for researchers and clinicians to develop better diagnostic and therapeutic strategies. Starting with an examination of the fundamental biochemical and molecular mechanisms of PCOS, this book discusses future trends based on recent research findings.

In addition to addressing core topics related to PCOS, the book is designed as a resource for scholars and researchers who study the impacts of this syndrome across various disciplines such as women's health, endocrinology, gynecology, psychology, and genetics. Furthermore, this book will address current treatment protocols, which are crucial for the clinical management of PCOS and raising awareness for patients, and will shed light on potential areas of research in the future.

We hope that this book serves as a resource for all researchers and health professionals who aim to contribute to scientific research on PCOS and help in a better understanding of this important subject.

Lastly, we would like to extend our gratitude to the authors and editors who contributed to the creation of this book. We appreciate their involvement in this vital project to disseminate scientific knowledge about PCOS to a broader audience.

We thank you for reviewing this book and extend our gratitude to everyone who contributes to a better understanding of PCOS.

Kind regards,

CHAPTER I

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF PCOS

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Polycystic ovary syndrome (PCOS) is considered one of the most common endocrine/metabolic disorders in women. Its prevalence depends on the diagnostic criteria used, as each criterion includes a varying number of PCOS phenotypes.

In a 2016 meta-analysis of 24 population studies, PCOS rates (and 95% confidence intervals) by diagnostic criteria in unselected populations were as follows:

*National Institutes of Health (NIH) – 6% (5-8%, n=18 studies)

*Rotterdam criteria – 10% (8-13%, n = 15 studies)

*Androgen Excess and PCOS (AE-PCOS) Association criteria – 10% (7-13%, n = 10 studies) [1]

Therefore, the closest estimate for the prevalence of PCOS would be about 6 percent, but the true prevalence is probably closer to 10 percent in women of reproductive age. However, because the disorder is primarily hereditary, this prevalence is likely reflected in the entire female population, regardless of age. [1]

RISK FACTORS

Conditions associated with an increased prevalence of PCOS

▪ Oligoovulatory infertility
▪ Obesity
▪ Diabetes mellitus (type 1, type 2, gestational)
▪ History of premature adrenarche
▪ First-degree relatives with PCOS
▪ Ethnicity (Mexican American, Australian aborigines)
▪ Drugs (valproate)

PCOS: polycystic ovary syndrome.

Table 1. [2]

HIGH RISK GROUP

***Oligoovulatory infertility** [3]

***Obesity and/or insulin resistance and gestational diabetes mellitus** [4]

***History of premature adrenarche** [5]

***First-degree relatives with PCOS** [6]

***Certain racial/ethnic groups** (e.g., Mexican Americans, Native Australians) compared to white or African American women [7,8]

***Use of antiepileptic drugs**

The frequency of PCOS increases in women with epilepsy who use antiepileptic drugs. While some studies suggest that this association is independent of medications, most available data now report that the increased rate of PCOS in these women is due to antiepileptic drug use, particularly valproate. [9 , 10] The strongest evidence comes from a meta-analysis of 11 studies showing a twofold increased risk of developing PCOS in 556 women treated with valproate compared with 593 women treated with other antiepileptic drugs. Remarkably, valproic acid appears to potentiate androgen biosynthesis in theca cells. [11]

PATHOPHYSIOLOGY

Figure 1. Summarized scheme regarding the pathophysiology of PCOS. Abbreviations and symbols: ↑ (increased), ↓ (decreased), DNA (deoxyribonucleic acid), GnRH (Gonadotropin-releasing hormone), IL-6 (interleukin 6), IR (insulin resistance), LH (luteinizing hormone), PCOS (polycystic ovary syndrome), SHBG (sex hormone-binding globulin), TNF-α (tumor necrosis alpha).

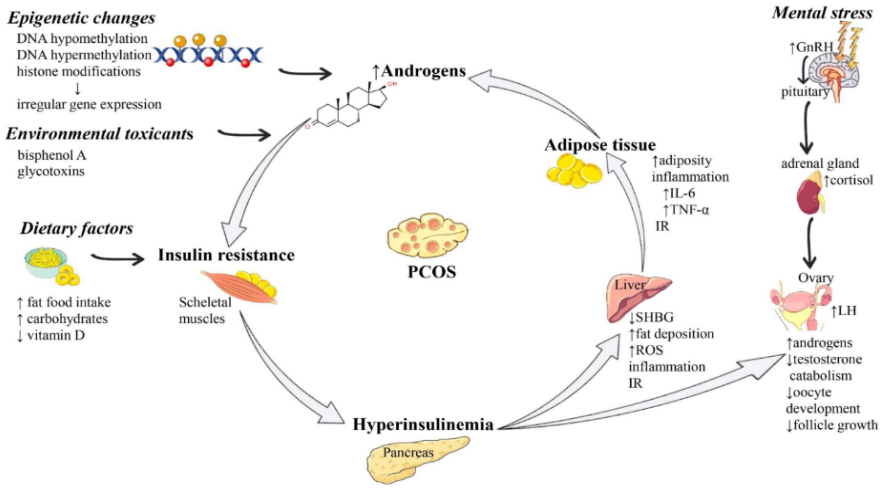

Figure 1. Pathophysiology of PCOS [12]

In a normal cycle, the concentration of hormones changes constantly, on the contrary, in chronic anovulation the endocrine environment remains stable. In PCOS, gonadotropin and sex steroid hormone levels characteristically vary little throughout the cycle.

Average daily androgen and estrogen production is increased in PCOS. As a result, serum testosterone, androstenedione, dihydroepiandrosterone (DHEA), dihydroepiandrosterone sulfate (DHEA-S), 17-alpha hydroxyprogesterone (17-OHP) and estrone increase.

Synthesis of testosterone, androstenedione and 17-alpha hydroxyprogesterone occurs in the ovary and is LH dependent. Synthesis of dihydroepiandrosterone (DHEA) and dihydroepiandrosterone sulfate (DHEA-S) is made in the adrenal gland. [13 ,14]

Serum estrone concentration also increases due to peripheral conversion of androstenedione. However, estradiol levels remain in the range of the early follicular phase. [15] This indicates inadequate development of the follicles and a persistently low production of estradiol. [16]

Contributors to ovarian dysfunction are alteration in the gonadotropin secretion pattern, hyperandrogenemia, and, but not always, insulin resistance. The change in GnRH release pattern results in an increase in LH pulsation frequency and relatively low FSH levels. LH-mediated androgen production increases in the ovarian stroma, follicle development disorder occurs and chronic anovulation occurs.

Insulin resistance and resulting increased insulin levels maintain hyperandrogenism. Increased androgen production in the ovary, decreased hepatic SHBG production, hyperinsulinemia and subsequent hyperandrogenemia create a chronic cycle.

PCOS is a complex and chronic disorder that affects muliple organs and systems. Gonadotropin secretion, insulin secretion, body weight and energy regulation, androgen excess; It contributes to a range of metabolic conditions that affect a variety of women's health conditions and lead to lifelong risks. [17]

GONADOTROPIN SECRETION AND ITS EFFECT

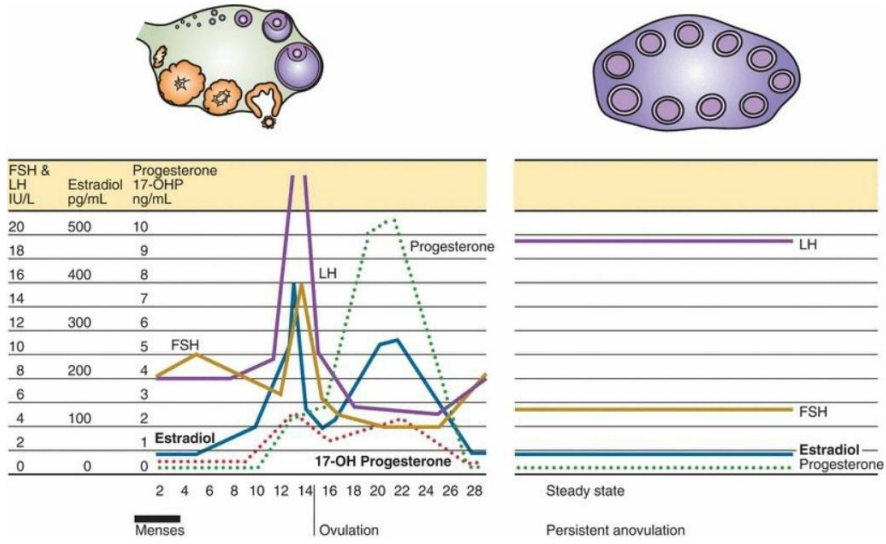

Figure 2 . Changes in sex hormone levels in PCOS [18]

Compared to women with normal cycles, increased LH concentration is seen in women with PCOS. FSH levels are low or normal; LH/FSH ratio increased. [19,20]

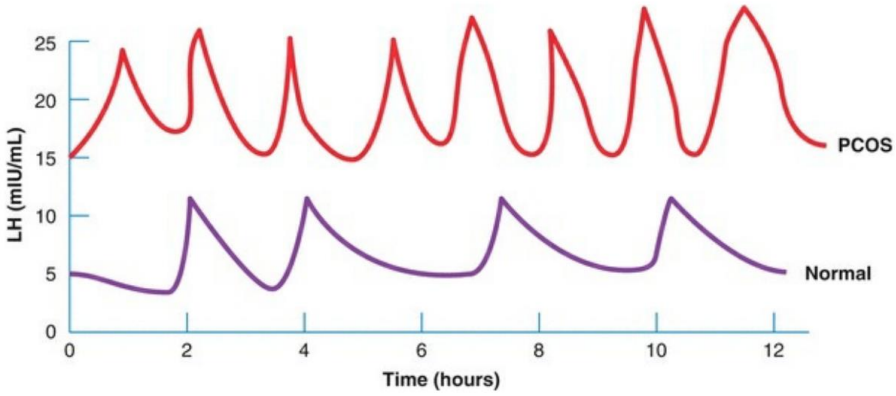

Figure 3. Changing concentrations of LH in the PCOS [21]

The reason for the increase in serum LH levels is; It is an increase in LH pulse frequency and a small increase in LH amplitude. [22] Decrease in FSH levels; The increase in GnRH oscillatory frequency is associated with a negative feedback of increased estrogen concentration, and slightly increased Inhibin-B (derived from small follicles) levels. [23]

In women with PCOS, the LH surge frequency does not show the normal cyclic variability as in ovulatory women, but oscillates approximately hourly and is relatively constant. The pattern in LH secretion is similar to the increase in GnRH pulse frequency. [24,25]

An exaggerated LH response to exogenous GnRH occurs in women with PCOS, and this response is lower in obese women compared to thin women. In obese women with PCOS, LH release amplitude and serum LH level are lower than in lean women. In addition; In in vitro bioassay systems, in addition to increased serum LH levels, an increase in LH bioactivity has been observed in patients with PCOS. In other words, the alkaline LH isoform, which has higher bioactivity, is dominant in PCOS patients. [26 , 27]

ETIOLOGY

EXTERNAL FACTORS	INTERNAL FACTORS
Epigenetic/Genetic Mechanism	Insulin Resistance
Environmental Toxicants	Hyperandrogenism
Physical and Emotional Stress	Inflammation
Diet	Oxidative Stress
	Obesity

GENETIC / EPIGENETICS

PCOS is a complex genetic disease similar to cardiovascular disease, type 2 diabetes, and metabolic syndrome, in which multiple genetic variants and environmental factors interact to enhance the development and characteristics of the disorder.

The hereditary basis for PCOS has been established by studies in twins and reports showing an increased prevalence of PCOS in first-degree relatives of affected women. [28, 29 ,30]

LH/choriogonadotropin receptor (LHCGR) is responsible for steroid production in theca cells. Hypomethylation of this receptor causes increased gene expression and LH sensitivity. [31]

In addition, hypomethylation of the promoter region of the epoxide hydrolase enzyme (EPHX1 - the enzyme responsible for the degradation of aromatic compounds) gene increases the enzyme activity. Increased production of EPHX1 reduces the conversion of testosterone to estradiol, thus contributing to PCOS. [32]

It has been shown that these and many similar enzymes contribute to the formation of PCOS through epigenetic mechanisms.

The genetic/epigenetic aspect of PCOS will be explained in detail in a separate chapter later in the book.

ENVIRONMENTAL TOXINS

Endocrine-disrupting chemicals (EDC), according to the definition of The United States Environmental Protection Agency (USEPA), are agents that cause changes in the synthesis, secretion, transport, binding, action or elimination of hormones.

EDCs act as hormone agonists or antagonists. Toxins and their mechanisms of action will be discussed in detail in the later chapters of the book.

STRESS

Chronic stress causes hypertrophy and hyperplasia in adipocytes. Chronic stress causes adipokine release and activation of stromal fat immune cells. [33]

Additionally, stress; It increases the release of inflammatory cytokines such as IL-6 and TNF-α, disrupting the oxidant-antioxidant balance. It stimulates the release of cortisol by affecting the HPA axis. It increases cortisal visceral fat tissue, stimulates gluconeogenesis, increases lipolysis, increases insulin levels and additionally reduces the level of AMH and affects the levels of sex hormones. [34, 35]

PCOS is a chronic disease that itself has negative effects on self-confidence and mental health. PCOS causes stress, and stress causes PCOS development, creating a cycle.

DIET

Although the current contribution of nutrition to PCOS is unclear, studies have shown a relationship between some nutrient levels and PCOS indices.

Saturated fatty acids (SFA) reduce insulin sensitivity and create an inflammatory environment by increasing the levels of some cytokines such as TNF-a. [36]

Vitamin D deficiency increases PCOS and its effects. Calcitriol upregulates insulin receptors at the mRNA and protein levels and increases insulin receptor sensitivity directly and indirectly. In addition,

vitamin D deficiency contributes to the PCOS mechanism by creating a pro-inflammatory environment. [37]

The relationship between PCOS and diet will be discussed in detail in the following sections of the book.

INSULIN RESISTANCE

In a study conducted for the first time in 1980, it was shown that insulin resistance, hyperinsulinemia and the insulin mechanism play an important role in the pathogenesis of PCOS. A significant correlation was shown between basal plasma insulin, androstenedione, testosterone levels, and insulin and testosterone levels after oral glucose load. [38]

Insulin resistance is especially seen in obese women with PCOS. While insulin resistance is detected in 70-80% of obese patients diagnosed with PCOS, this rate is 20-25% in thin patients with PCOS. [39,40] Similar to diabetic patients, insulin sensitivity in PCOS patients is reduced by 35-40% compared to normal women. [41] 35% of patients with PCOS have impaired glucose tolerance and 7-10% meet criteria for Type 2 diabetes. [42] Women with Type 2 diabetes have been found to be 6 times more likely to be diagnosed with PCOS compared to non-diabetic women of similar age and weight. [43] Insulin resistance causes an increase in the hydrolysis of stored triglycerides in adipose tissue and in the level of free fatty acids in the circulation. Blood glucose levels increase as a result of decreased glucose utilization and increased gluconeogenesis in the liver. As a result, compensatory hyperinsulinemia occurs.

After 75 grams of oral glucose loading in normal healthy women, insulin reaches its maximum level within 30 minutes and then the insulin level decreases until the 2nd hour. In women with PCOS,

insulin levels are both increased and spread over a longer period of time:

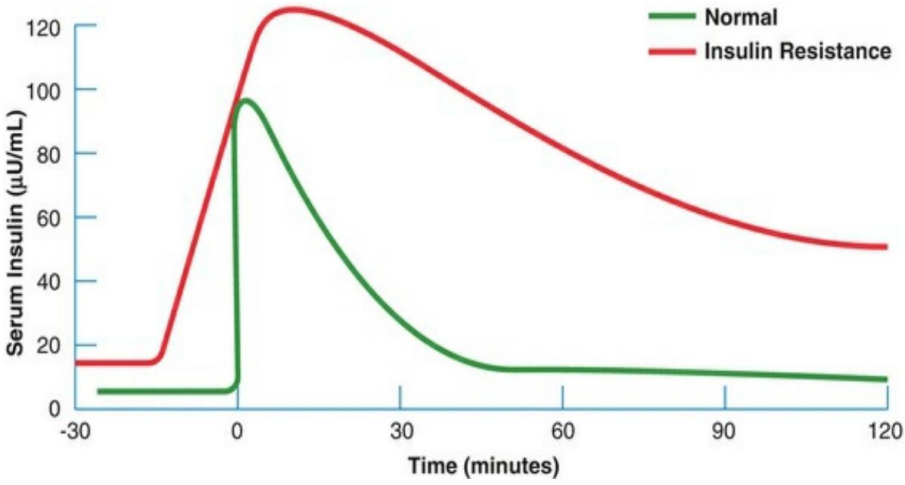

Figure 4. 75 gr oral glucose test insulin levels in normal and insulin resistance [44]

Increased insulin levels;

- It stimulates androgen production from theca cells in the ovary. (At the same time, insulin sensitivity increases in theca cells)
- It causes hyperandrogenemia by inhibiting SHBG production from the liver.
- Increases the effect of LH, increases androgen production by acting similar to insulin and LH [45]

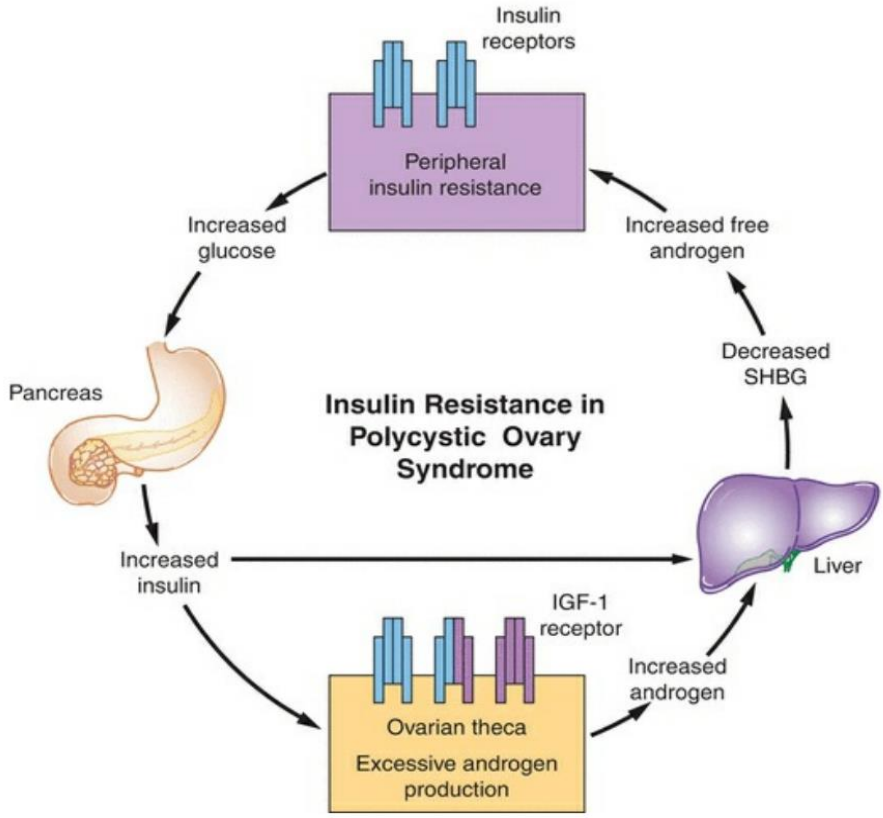

Figure 5 . Mechanism of insulin resistance in PCOS [44]

High insulin levels reduce SHBG production, free androgen levels rise and insulin resistance gradually worsens. This continues in a cycle.

Finally, it should be noted that insulin resistance may not be seen in 25-50% of women with PCOS. Hyperinsulinemia and insulin resistance are not the main cause or pathogenic factor for all women with PCOS.

OBEZITY

In obese women, insulin resistance increases and hyperinsulinemia occurs as a response. [46] Obesity ; Visceral fat tissue, in particular, is the cause of inflammation in itself, causing an increase in cytokines such as TNF-a, IL-6, leptin and resistin. [47]

Obesity itself creates a PCOS-like condition;

*HHO axis disorder → decreased hepatic SHBG production → increased testosterone levels → hyperandrogenism

*Increase in estrogen level → LH frequency and amplitude increases → FSH release is inhibited

Obesity poses a moderate risk for PCOS and strengthens the cycle by increasing hyperinsulinemia and insulin resistance in women with PCOS [48] The relationship between PCOS and obesity will be examined in detail in the later chapters of the book.

INFLAMMATION

Optimal inflammation is the main factor for oocyte development. But high WBC, CRP levels are associated with PCOS. CRP increases the release of pro-inflammatory cytokines from the liver and monocytes. Proinflammatory molecules reduce GLUT-4 expression, decreasing glucose reuptake. [49] TNF-α stimulates theca cell proliferation, causing insulin resistance and hyperandrogenism. [50] It blocks IL-1, FSH and LH receptors, preventing follicle development and ovulation. [51]

HYPERANDROGENISM

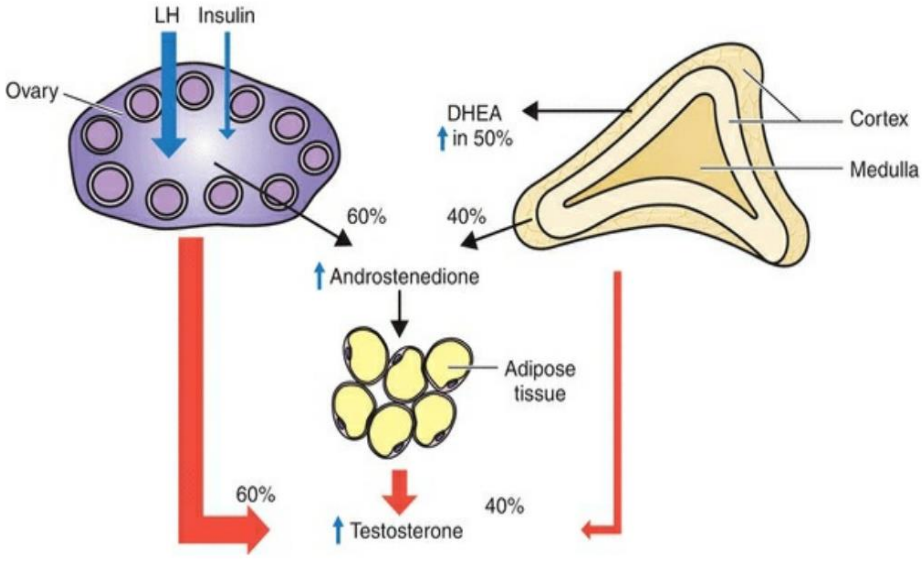

Figure 6. Increased LH secretion and its effect on sex steroid production [44]

Irregular LH secretion → increased LH stimulation and bioactivity → ovarian production of testosterone and androstenedione

In another opinion; The reason for this is that a greater amount of testosterone is secreted in the theca cells, which naturally increase in volume in the increased ovarian stroma. [52,53]

Adrenal androgen production also increases in PCOS; DHEA, DHEA-S, andrsotenedione levels increased in more than half of the patients. [54] Several hypotheses have been proposed for the increase in adrenal androgen production;

*chronic estrogen elevation may reduce adrenal 3B-HSD effectiveness.[56]

*There is an increase in the release of ACTH from the pituitary or there is increased sensitivity to ACTH [57]

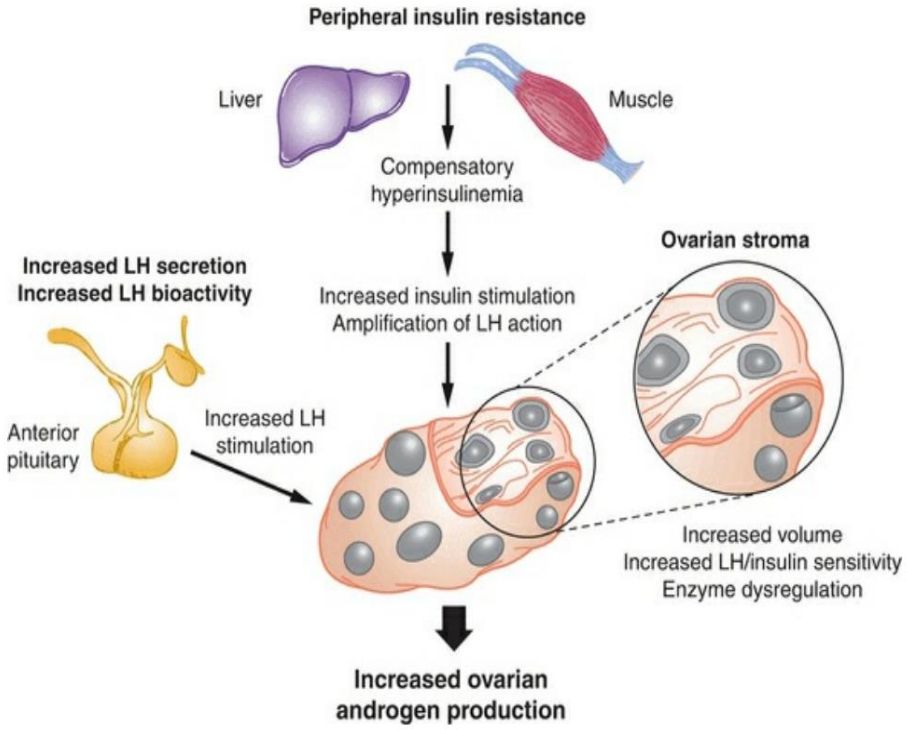

Figure 7.

High androgen levels inhibit FSH-induced LH receptors in granulosa cells. Follicular development is interrupted in the early phase. New follicle formation continues, but maturation cannot occur. With increased LH activity, many small follicular cysts are seen, most of which are luteinized. These follicles are surrounded by theca cells that have increased in size, and the follicles that undergo atresia increase the volume and gradually thicken the ovarian stroma. Cases in which spontaneous ovulation was achieved after ovarian wedge resection; supports this view. With these facts; It was also concluded that the increased andogenous environment in the ovarian environment prevents follicle development and ovulation. [58]

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CHAPTER II

POLYCYSTIC OVER SYNDROME DIAGNOSTIC CRITERIA AND DIFFERENT PHENOTYPES

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POLYCYSTIC OVER SYNDROME DIAGNOSTIC CRITERIA AND DIFFERENT PHENOTYPES

PCOS prevalence appears similar across ethnicities and is 10-13% globally by International guideline/Rotterdam criteria (Bozdag vd., 2016). The currently accepted theory in its etiology is the 'two hits' theory. According to this, it is firstly exposed to virilization or hyperandrogenism in the intrauterine period and secondly, to be activated by insulin resistance developing in the postnatal period (Bremer, 2010).

Many people are misdiagnosed or delayed due to the lack of a standard diagnosis, ethnic differences, and marked clinical variations in the course of the disease. It increases susceptibility to conditions such as insulin resistance, diabetes mellitus type 2 , dyslipidemia, hypertension, cardiovascular diseases and endometrial cancer in the long term (Calan vd., 2016). For this reason, a standardization of diagnosis and treatment is required. The most up-to-date of these studies is the *'2023 International Evidence-Based PCOS Evaluation and Management Guidelines'* (2023 PCOS Guidelines) in partnership with the *'European Society of Human Reproduction and Embriology*' (ESHRE) and *'American Society of Reproductive Medicine*' (ASRM).

When looking at the criteria used in the diagnosis absolutely of PCOS, the most used criteria are the ESHRE/ASRM criteria, which were published in 2004, known as the "Rotterdam Criteria" (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). When we examine criteria, the presence of two of the criteria of clinical and/or biochemical hyperandrogenism, oligoovulation or anovulation, polycystic ovarian image or increased serum AMH level is sufficient for a definitive diagnosis. However, it has been discussed because it does not include different phenotypes and considers those with and without hyperandrogenism together.

In 2006, the "*Androgen Excess Society*" (AES) criteria were determined, in which only hyperandrogenemic individuals were diagnosed with PCOS. Accordingly, the diagnosis is made when both clinical and/or biochemical hyperandrogenism and ovary dysfunction and/or polycystic ovary diagnostic criteria are met (Azziz vd., 2006).

According to the most up-to-date 2023 PCOS Guidelines, clinical and/or biochemical hyperandrogenism and menstrual dysfunction are sufficient for the diagnosis. While ultrasound image is not necessary in the adolescent group, being positive in the adult group is a supportive finding (Mousa vd., 2023).

When looking at phenotypes according to the Rotterdam criteria;

Full phenotype Phenotype A: Oligo/anovulation + hyperandrogenism + polycystic ovarian morphology

Phenotype B: Oligo/anovulation + hyperandrogenism

Phenotype C: Hyperandrogenism + polycystic ovarian morphology

Phenotype D: Oligo/anovulation + polycystic ovary morphology.

It has been stated that each PCOS phenotype has different metabolic risks and phenotypes A and B are more related with metabolic and cardiovascular risk due to the hyperandrogenism component (Azziz vd., 2009).

1. Menstrual Dysfunction

In order for a menstrual cycle to be called oligomenorrhea, less than 9 menstrual cycles must be seen in a year, while in order to be called amenorrhea, it must not have menstruation for at least 3 sequential months.

According to the 2023 PCOS analysis, the definition of irregular menstrual cycle is standardized and includes the following criteria:

- It is normal in the first year after menarche.
- Between 1-3 years, 21 days less or 45 days longer after menarche,
- 21 days less or 35 days longer (or less than 8 cycles per year) from menarche to 3rd letter perimenopause,
- Any cycle lasting longer than 90 days from the 1st year after menarche and/or
- Defined as primary amenorrhea by the age of 15 or 3 years after thelarche.

2. Hyperandrogenism

In PCOS diagnostic criteria, hyperandrogenism can be classified as biochemical or clinical. The parameters that can be used in the diagnosis of biochemical hyperandrogenemia are: *'calculated biyoavailable testosteron',* '*calculated free testosteron*' ve *'free androjen indeks' (FAI).* Up to 30% of PCOS cases may have elevated dehydroepiandrosterone sulfate (DHEAS), but there is no definite opinion about its diagnostic contribution and the clinical significance of isolated DHEAS elevation (Alataş vd., 2019). Free testosterone measurement is a more sensitive parameter than total testosterone in showing androgen excess (Goodman vd., 2015).

In the 2023 PCOS guide recommendations, it is stated that direct testosterone measurements are not reliable. It has been stated that the testosterone measurement should be standardized with further studies. However, it is emphasized that the "*free androgen index* (FAI)" calculation is frequently used and it is recommended to use the calculation of "*calculated free testosterone*" or FAI in the evaluation of biochemical hyperandrogenemia. (Mousa vd., 2023).

For clinical hyperandrogenism, many guidelines emphasize that hirsutism, alopecia and acne are obvious signs for clinical hyperandrogenemia. It is the modified Ferriman-Gallwey (mFG) scale recommended for the diagnosis of hirsutism. Although it may differ

according to ethnicity, a score above 4-6 suggests a clinical diagnosis of hirsutism (Mousa vd., 2023). Especially after the Rotterdam criteria, the value of these signs and symptoms in adolescence has also been discussed. The opinion of the AES on this issue is that only hirsutism should be considered in the adolescence period and the presence of acne should not be used in a diagnostic sense. However, it has also been suggested that severe or unresponsive acne in adolescence may be associated with the development of PCOS in 40% of cases in the future (Cannavò vd., 2004).

3. Polycystic Ovary Morphology

Diagnostic criteria for polycystic ovarian morphology is the most discussed topic. Looking at the criteria in this regard:

- Follicle number per ovary (FNPO) ≥ 20 in at least one ovary should be considered the threshold for PCOM in adults
- Ovarian volume (OV) ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in at least one ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary.
- It is seen as the absence of cyst, corpus luteum and dominant follicle.

In the recommendations of the 2023 PCOS guideline, it is recommended to make significant changes about PCO morphology. Looking at these changes:

- Evaluation of PCO morphology is not recommended until 8 years after menarche.

- New age-related cut-off values should be determined, but no definition has been made on this subject.

4. Anti Müllerian Hormone

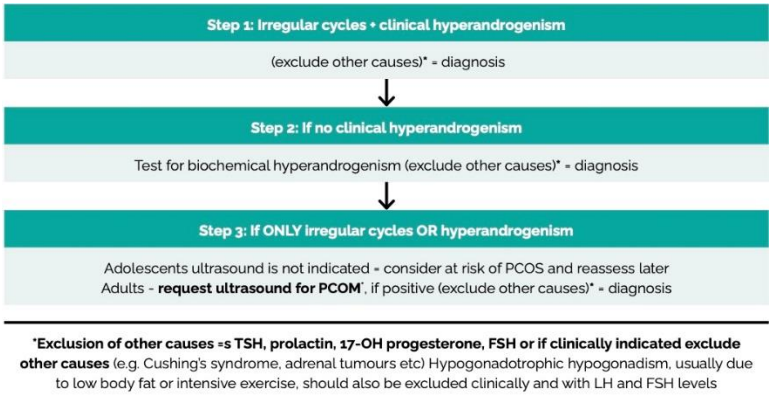
Anti-mullerian hormone (AMH) is a polypeptide. It belongs to the "Transforming growth factor-beta (TGF-β)" family, which is released only from the granulosis of preantral and small antral follicles. AMH reaches its maximum level between the ages of 20-25. There is no threshold value determined by age and ethnicity. If the BMI is high and oral contraceptives are used, the results may be wrong according to the menstrual cycle time.

AMH has been suggested as an alternative marker to identify ovulatory dysfunction in PCOS patients, and moreover, it is thought to predict PCOS pathogenesis and different phenotypes (Cassar vd., 2014). In the AES 2016 recommendations, it is stated that increased AMH value (>4.5 ng/mL) can be used instead of PCO morphology in cases where sufficient ultrasound cannot be performed.

The 2023 PCOS guideline recommendations do not recommend using serum AMH levels as a single test in the diagnosis of PCOS.

In conclusion, accurate diagnosis is important because polycystic ovary syndrome is a complex disease with metabolic, endocrinological, psychiatric and cardiovascular effects.

Figure 1: Screening, diagnostic assessment



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CHAPTER III

GENETICS & POLYMORPHISM IN POLYCYSTIC OVARY SYNDROME

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1. Introduction

Polycystic ovary syndrome (PCOS) is a complicated polygenic disease that may be influenced by a complex interplay of environmental conditions, genetic predispositions, and protective genomic polymorphisms. It is also difficult to diagnose menopausal women, premenarchal girls and teenage girls. The cause of PCOS is still a mystery despite decades of research. Current diagnostic criteria do not adequately account for the underlying biological distinctions associated with various kinds of PCOS, according to genomic studies of the condition. These studies have also shed vital light on disease pathways. The existence of mutations and/or polymorphisms has been found in several genes that have been postulated to be involved in the etiopathogenesis of PCOS, suggesting that the condition has a significant heritable component.

Although many explanations have been brought out, ranging from inheritance to environmental exposure, both in utero and in the postnatal life, the exact aetiology and pathophysiology of PCOS are still a subject of current research (Goodarzi et al., 2011). According to Diamanti-Kandarakis et al. (2006), PCOS is regarded as a polygenic condition, and both genetic and environmental variables are significant in its development. Studies involving twins and families with PCOS point to heritability and a solid genetic foundation

(Vink et al., 2006). Candidate genes for PCOS have been found to be linked in the androgen biosynthesis pathway, insulin resistance, and chronic inflammation. According to Zhao et al. (2015), the route of

inheritance for PCOS has not yet been conclusively determined. Additionally, results from candidate gene research are conflicting.

2. Evidence for a genetic background

PCOS may have a hereditary component, according to familial clustering of PCOS cases. As a result of the interaction between susceptibility genes and environmental factors, PCOS frequently exhibits a non-Mendelian pattern of inheritance that is consistent with a complex genetic architecture, comparable to that of type 2 diabetes and obesity. There are rare Mendelian forms of PCOS linked with severe phenotypes. In the 1960s, it was first proposed that PCOS may have a genetic cause. Systematic research on the relatives of women with PCOS revealed a familial clustering of the syndrome's reproductive symptoms, which is consistent with a hereditary vulnerability to these abnormalities (Dapas & Dunaif, 2022). The substantial heritability of biochemical traits in probands and affected sisters, despite large variability in symptoms, shows that these biochemical traits are significantly impacted by hereditary factors. Moreover, and maybe more significantly, polycystic ovarian morphology is a marker of hereditary features in PCOS families (Franks et al., 2008). Twins are particularly useful since they share the same environmental factors and can be used to estimate trait heritability. Researchers can measure heritability by simply comparing trait correlations between pairs of monozygotic twins (they have identical DNA), to those between pairs of dizygotic twins, who have a 50% DNA share (Vink et al., 2006).

Cytogenetic methods have not discovered substantial chromosomal abnormalities. Indeed, there was no difference in the aneuploidy frequencies of unfertilized oocytes between PCOS sufferers and those with tubal factor infertility. Although linkage analysis and association have both been employed by academics to investigate the genetics of complex traits, they have not shown to be very fruitful. The poor results of such investigations into the genetic causes of PCOS further hints that it is a complicated genetic condition. Researchers could look at more genetically homogeneous founder populations or conduct family-based association studies, which only need a proband and typically both parents. There are currently a number of whole genome techniques available that do evaluate the function or location of potential genes in PCOS. All exons or the entire genome can now be sequenced using next-generation technologies, making this a feasible alternative for researching PCOS' genetic roots. Finding a significant variant is only the first step, of course. It is important to use molecular genetic studies to confirm the biological relevance of PCOS-associated abnormalities (such as targeted genetic disruption in cell culture). There is a serious issue with all noteworthy findings from genome-wide association studies (GWAS), which is that this subsequent stage is rarely performed in studies (Dumesic et al., 2015).

3. Detecting genetic variation

Researchers first used candidate gene analysis to start understanding the genes causing PCOS. The candidate gene approach investigates genes chosen for their potential contribution to PCOS. SNPs or microsatellites within a gene of interest are used in candidate gene

analyses to assess whether the gene is linked to PCOS, or to specific PCOS features or phenotypes, in populations or in families. Generally speaking, regions (loci) governing (i) gonadotropic secretion and action; (ii) steroid biosynthesis and action; (iii) folliculogenesis); (iv) insulin action; (v) weight and energy management have been the focus of candidate genes examined in PCOS. Multiple restrictions have impeded research on PCOS potential genes, including: (i) a lack of understanding of PCOS's basic pathophysiology; (ii) the complexity of the disorder, which indicates that either many genes or a complex genetic architecture are involved; (iii) only one or two variations from each important gene are genotyped; (iv) the heterogeneity of the PCOS phenotype; (v) the incomplete characterization of the phenotype in family members; (vi) the lack of suitable controls; and (vii) more recently, an effort has been made to overcome these restrictions by including larger numbers of better phenotyped subjects and controls, as well as both discovery and independent replication cohorts (where the findings are confirmed or not) (where the candidate gene is first studied and positively identified) (Mykhalchenko et al., 2017).

Some of the most well-known potential genes investigated include those for the insulin receptor (INSR) and fibrillin-3 (FBN3) proteins, as well as those for obesity and diabetes (type 2). PCOS is characterised by insulin resistance and the compensatory hyperinsulinemia that results from this, which increases the risk of impaired glucose tolerance and T2DM in women with PCOS. According to studies, up to 30–40% of PCOS-affected women have reduced glucose tolerance, and up to 10% of them acquire type 2 diabetes by the age of 40 (Moran et al.,

2010). Given that the majority of PCOS patients have insulin resistance and that the ovarian stroma, which includes theca and interstitial cells, releases androgens in response to stimulation with higher insulin levels, the INSR has been an obvious candidate gene target (Altchek et al., 2003). Linkage between PCOS and INSR has since been reported in several studies such as Stewart et al., (2006); Ewens et al., (2011); Mukherjee et al., (2009); Xu et al., (2011).

Despite conflicting findings (Prodoehl et al., 2009; Wojciechowski et al., 2012; Qi et al., 2014), fibrillin malfunction may be responsible for the increased stromal collagen and enlargement of the ovarian cortex frequently seen in PCOS. The majority of candidate gene studies have not found a connection between PCOS and genes related to obesity, although they do imply a connection between the PCOS adiposity genes MC4R (Melanocortin 4 receptor) and FTO (Fat Mass and Obesity-Associated) (Louwers et al., 2013; Ewens et al., 2011). A meta-analysis involving 2,548 PCOS patients further supported the relationship between FTO SNPs and increased body mass Wojciechowski et al., (2012); Qi et al., (2014). However, recent family studies found that the MTNR (melatonin receptor) gene was linked to PCOS in Han Chinese PCOS family groups (Song et al., 2015; Zhang et al., 2014).

4. Linkage analysis

To find disease loci, linkage analysis can be performed to family data. Co-segregation patterns can be examined and specific alleles can be linked to various characteristics by quantifying polymorphic sequences

in large families (for example, using polymerase chain reaction). Linkage analysis simply analyses the relative frequencies with which alleles at various loci are shared across relatives, regardless of whether an inheritance model is specified or a nonparametric technique is used. Theoretically, relatives with the same disease variants are more likely to share a haplotype than those with different disease variations. Linkage analysis can be used to pinpoint specific genomic areas where specific disease variations are routinely found (Pericak-Vance, 1996). Linkage analyses are excellent for researching Mendelian diseases that are substantially inherited, but they are less useful for researching complicated features (Dapas & Dunaif, 2022).

5. GWAS

After the human genome was sequenced, a new age of genetic research began with the establishment of commercial genotyping arrays that could concurrently test many 100.000 of common DNA variants. With the advent of affordable association testing over the entire genome, a priori theories regarding potential disease genes were no longer necessary. The term "genome-wide association studies" (GWAS) was coined for these investigations. Individual genetic risk assessment for complicated diseases has been made possible by GWAS. A polygenic risk score can be generated for a specific person by taking into account the combined impact from trait-associated variations throughout the genome. However, the heritability of a disorder and the amount of underlying genetic risk that has been revealed by GWAS limit the predictive potential of polygenic risk scores intrinsically which is a

limitation for PCOS given the limited sample sizes studied to date (Khera et al., 2018).

As the analyses do not rely on a biological mechanism hypothesised a priori, GWAS provides a crucial tool for disorders whose pathophysiology is less certain, such as complex genetic characteristics, including PCOS. As a result, GWAS research can lead to new theories. New genes have been discovered by GWAS that may be involved in the aetiology of PCOS. GWAS identifies loci, not genes. The majority, but not all, of the candidate genes suggested at the linked loci found in the GWAS of PCOS were connected to hormones, insulin resistance, and organ growth. A few of these genes are GTF2A1L, LHCGR, C9orf3, FSHR, LOC100129726, THADA, ERBB4/HER4, GATA4, NEIL2, FDFT1, FANCC (Fanconi Anemia Complementation Group C gene), DENND1A, FSHB, ARL14EP (ARL14 effector protein gene), RAB5B, SUOX and INSR (Zeggini et al., 2008; Goodarzi et al., 2012; Stolk et al., 2012; Sun et al., 2016).

A significantly large number of individuals are needed for both discovery and replication in GWAS, despite the fact that it allows for hypothesis-free testing. Numerous loci identified by GWAS are engaged in transcriptional or translational efficiency rather than being mapped to recognisable open reading frames. Instead of rare variants with significant effects, GWAS is better fit for identifying common variations (>5% in a population) with modest effects. Even while GWAS studies have contributed significantly to our understanding of PCOS thus far, further research is still required. Other research might discover more loci, and finer mapping of known loci might find

particular genes and interesting functional variations. However, it is also necessary to look into other factors, such as chromosomal structural abnormalities and epigenetic changes, which may contribute to the high heritability of PCOS (Mykhalchenko et al., 2017).

6. Phenome-wide association studies

The phenome-wide association study (PheWAS), a newer type of genetic association study, has been made possible more recently by the integration of genomic data with electronic health information. In PheWAS, the paradigm is reversed so that a catalogue of phenotypes is systematically examined for association with a given SNP rather than systematically examining SNP associations with a given phenotype, as in a GWAS. ICD (International Classification of Diseases) codes or more precisely defined algorithm-based diseases are just two examples of phenotypes that could be included in a PheWAS. Genetic risk scores can also be assessed against a variety of phenotypes with PheWAS, therefore it is not necessary to limit it to single SNP relationships. The best tool for determining pleiotropic gene effects is PheWAS (Rastegar-Mojarad et al., 2015).

By examining the diseases that are linked to PCOS-susceptibility variations, phenome-wide association studies may help identify long-term health risks (Dunaif, 2016). PheWAS is yet another method for examining genomic overlap between diseases. Joo et al. (2020) examined the relationships between 1711 EHR phenotypes with ICD code classifications and a PCOS polygenic risk score derived from the most current PCOS meta-GWAS summary statistics (Day et al., 2018).

They discovered 13 phenome-wide signals that were repeated and had consistent directions of effect. Although some signals, such as "overweight" and "obesity" or "obstructive sleep apnea" or "sleep apnea" indicate the same diseases all of the significant connections seem to be connected to obesity.

7. Mendelian randomization

Mendelian randomization (MR) is an observational method that estimates the causal relationship between an exposure (such as overweight/obesity) and an outcome (such as the development of PCOS) by using genetic variants as instrumental variables. MR is less prone to reverse causation than any other observational approaches since variations are allocated randomly at conception (Dobbie et al., 2023). Mendelian randomization, which uses genetic polymorphisms to explore causation between exposures and outcomes, has been used by researchers to get beyond the drawbacks of observational studies. The inability of observational epidemiologic research to establish a causal relationship between two conditions is one of its limitations. Diverse factors may mediate an apparent association between PCOS and a certain comorbidity. Obesity, fasting insulin, testosterone levels, serum sex hormone-binding globulin concentrations, male-pattern balding, menopause timing, and depression may all be causal factors in PCOS, according to Mendelian randomization studies. In turn, PCOS may raise the risk of breast cancer that is oestrogen receptor-positive, lower the risk of ovarian cancer caused by endometrioid tissue, and have no direct causal connection to diabetes (type 2), stroke or coronary heart disease. (Zhu & Goodarzi, 2022).

8. LD score regression

The fundamental idea behind LD score regression is that the distribution of test statistics in a GWAS is a function of LD: Higher association statistics are observed for SNPs that are associated with a causal variation proportional to their relative LD with the causal variant. As a result, inflation of test statistics due to LD is taken into account, and a more precise estimate of confounding due to population stratification and/or cryptic relatedness can be obtained (Bulik-Sullivan et al., 2015). To do this, the association test data are regressed against the amount of genetic variation that each variant has been able to identify (its LD score). To further investigate the genetic overlap across variables, LD score regression might be expanded. Greater understanding of common biological pathways and causal linkages can be obtained by quantifying the additive genetic effects that are shared between phenotypes (Dapas & Dunaif, 2022). Day et al. (2018) used LD score regression in their extensive meta-analysis of PCOS to look at the genetic relationships between the condition and other variables. Strong genetic relationships between PCOS and BMI, fasting insulin, childhood obesity, type 2 diabetes, triglycerides, high-density lipoproteins level, and cardiovascular diseases were determined by the investigation.

9. Next-generation sequencing

NGS has been used in many different experimental methods, such as whole exome sequencing (WES), whole genome sequencing (WGS), targeted sequencing, RNA sequencing (RNA-seq), measuring genetic

variation across the genome, chromatin immunoprecipitation followed by NGS (ChIP-seq), and measuring genetic variation within protein-coding regions. NGS technologies have been employed in PCOS research in a variety of methods during the past few years, providing fresh insights into the genetic causes of the condition (Dapas & Dunaif, 2022). RNA-seq has been used in numerous investigations of PCOS-related pathways to evaluate gene expression in diverse tissues under varied circumstances. Several gene networks and pathways, including MAPK signalling (Liu et al., 2015; Hu et al., 2020), androgen receptor signalling (Wang et al., 2015), metabolic processes (Zhao et al., 2019), inflammatory and immune responses (Pan et al., 2018; Wang et al., 2019), have been identified as being disrupted in PCOS by these studies. However, it is challenging to distinguish between causative abnormalities and adaptive consequences of the disease in gene expression investigations (Walters & Handelsman, 2016). In an effort to link environmental exposures to transcriptional changes, researchers have started to trace DNA methylation alterations to gene expression changes in PCOS (Jones et al., 2015; Wang et al., 2014).

10. Candidate genes involved in pathophysiology of PCOS

Nearly 100 genes associated with PCOS susceptibility have been discovered through various genetic research. However, the precise function of these susceptibility genes has yet to be established. Polymorphisms in genes implicated in gonadotropin action, metabolic or regulatory pathways of steroid hormone synthesis, and insulin-signaling pathways have been studied as PCOS risk genes. PCOS is phenotypically expressed as a result of polymorphism in the

steroidogenesis pathway-related genes CYP11A, CYP17, CYP19, CYP21, and HSD (Chaudhary et al., 2021).

CYP17 (P450c17) uses the microsomal electron transport system and cytochrome P450 oxidoreductase to catalyse two mixed-function oxidase reactions. All steroidogenic organs exhibit CYP17 expression; however, certain species-related variations in the enzyme's expression have been noted in the placenta and adrenal gland. Although luteal cells and granulosa cells do not express CYP17, a recent study (Moran et al., 2003) contends that human luteinized granulosa cells in culture do. In addition to higher transactivation of the CYP17 promoter, it has been demonstrated that PCOS women's ovarian theca cells exhibit increased P450c17 enzyme expression and activity (Wickenheisser et al., 2004). Studies have also revealed that the PCOS theca cells' dysregulated CYP17 expression of mRNA stability (Wickenheisser et al., 2005).

As the first and rate-limiting enzymatic step for biosynthesis of steroid hormones, CYP11A catalyses the conversion of cholesterol to pregnenolone. The results of a meta-analysis showed a relationship between PCOS and a pentanucleotide repeat polymorphism in the promoter of CYP11A1 (Yu et al., 2014). Furthermore, the link between this gene and hirsutism and the lack of a substantial link to ovulatory function suggest that CYP11A have a major function in the emergence of hirsutism in PCOS (Chaudhary et al., 2021).

Androstenedione and testosterone, which are C19 androgens, are converted into estrone and estradiol, which are C18 oestrogens, by the enzyme CYP19 (P450arom). The ovary, adipose stromal cells, the

placenta, the bone, and numerous foetal tissues are where P450arom is primarily expressed. According to numerous research, individuals who have hyperandrogenism have insufficient aromatase activity (de Medeiros et al., 2015). Furthermore, both lean PCOS women and obese PCOS women experience a considerable decline in P450arom activity (regardless of their BMI) (Chen et al., 2015). Numerous studies have linked the aromatase enzyme to hyperandrogenism, and androgen biosynthesis plays a crucial role in the development of PCOS as CYP19 is a vulnerable gene (Chaudhary et al., 2021).

Both androgens and oestrogen are bound by the Sex hormone-binding globulin (SHBG). One could think of SHBG as a potential gene essential to the PCOS pathophysiology. Women with condition of PCOS are thought to have higher levels of androgen and are frequently insulin resistant and have compensatory hyperinsulinemia, which prevents the hepatic production and SHBG secretion and lowers the amount of SHBG in the blood. Low serum SHBG levels have been linked to hyperandrogenic symptoms in PCOS women, including acne, hirsutism, virilization and androgenic alopecia (Davison et al., 2005). Additionally, some typical genetic changes in the SHBG gene affect the amount of SHBG in the blood and may be linked to the PCOS phenotype (Xita & Tsatsoulis, 2010).

Chromosome 6p21.3 is the location of CYP21 (P450c21). The sole location where CYP21 is primarily expressed is in the adrenal cortex, which is essential for producing the cortisol, corticosterone, and aldosterone. Studies have shown that women with symptoms of hyperandrogenism, early pubertal development, and PCOS-like

phenotype are more likely to be heterozygous for the CYP21 gene mutation (Witchel & Aston, 2000). Although the CYP21 gene and mutations on it do not appear to have a major impact on the susceptibility to PCOS, they may have a little impact that can be resolved by additional research (Chaudhary et al., 2021).

Androgen receptors (AR) promote the actions of androgen. Increased androgen levels have been linked to anovulation, irregular menstruation, and the formation of microscopic cysts in the ovaries. In experimental animals, exposure to intrauterine androgens promotes the development of the PCOS phenotype in adulthood (Xita & Tsatsoulis, 2006). The genetic variation in exon 1 of the AR gene, which has CAG repeats, suggests a connection between the incidence of PCOS and AR activity (Schüring et al., 2011). Short AR CAG repeats are more common in PCOS women, according to studies, and they may have a role in the development of the condition in both Caucasian and Chinese populations (Lin et al., 2013). Additionally, this mutation increases androgen sensitivity and AR overexpression in PCOS patients (Shah et al., 2008).

The breakdown of androstenedione into estradiol and testosterone, the last stage in the production of an active gonadal steroid, is catalysed by the 17β-HSD enzymes. Studies have shown an increased prevalence of the 71A/G polymorphism in the promoter region of the 17β-HSD type 5 gene and its correlation with PCOS in Caucasian women. The accumulation of androstenedione carried on by the lack of this enzyme has also been linked to some menstrual abnormalities (Qin et al., 2006). One possible gene for the etiopathogenesis of PCOS is the

polymorphism of the 17βHSD type 5 gene, which may be significant in the emergence of hyperandrogenemia and insulin resistance (Chaudhary et al., 2021).

The INSR (insulin receptor) gene, which is found on the short arm of chromosome 19, is crucial for the metabolism of insulin. The INSR gene, which is an essential part of the insulin signalling system, has been linked in studies to the pathophysiology of PCOS, and as such, it may be a viable candidate gene for PCOS (Chaudhary et al., 2021).

G protein-coupled receptor on chromosome 2p21 named the folicle-stimulating hormone receptor (FSHR) is expressed in granulosa cells in a manner similar to the LHCGR. When FSHR binds to FSH, it induces oogenesis, gametogenes and follicle development, which leads to follicular maturation and granulosa cell proliferation. In the Chinese population and populations with European ancestry, the FSHR gene was linked to PCOS, according to a recent GWAS study (Mutharasan et al., 2013).

The majority of the results of the following genes linkage to PCOS have been inconsistent or contradicting: The StAR protein functions as transporter protein and is essential for moving cholesterol from the outside to the mitochondrial membrane at the start of the steroidogenesis process. By catalysing the dehydrogenation and isomerization reaction, the 3HSD enzyme is critical for active steroid hormone production. The LHCGR (luteinizing hormone/choriogonadotropin receptor) gene, a G-protein coupled receptor, is crucial for ovulation as a response to mid-cycle LH surge

and is mostly expressed in the preovulatory follicles' granulosa cells. The gonadotroph membrane of the anterior pituitary and numerous extra-pituitary tissues, including the ovary, placenta, breast, and cancer tissues, contain the G-protein coupled receptor known as the gonadotropin-releasing hormone receptor (GnRHR). One of the most important and versatile proinflammatory cytokines is interleukin 1 (IL-1). The PPARG (peroxisome proliferator activated receptor gamma) is a transcription factor that is activated by ligands. Neuropeptide Kisspeptin (KISS). A G protein-coupled transmembrane receptor called GPR54 is present in GnRH neurons, is activated by the Kiss 1 gene, which raises LH levels (Chaudhary et al., 2021).

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CHAPTER IV

POLYCYSTIC OVARY SYNDROME (PCOS) AND IMMUNOLOGY

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INTRODUCTION

Hormonal imbalances and immune cells play a role in the pathogenesis of PCOS, according to current data. Studies have focused on the causes and effects of chronic inflammation, particularly in women with PCOS. Understanding the factors with a role in the pathogenesis of PCOS, which has effects on hormonal and various metabolic systems, is important for the treatment and management of PCOS patients. Researchers have recently uncovered the relationship between the immune system and PCOS, and studies in this field are steadily increasing.

Many studies have demonstrated the presence of chronic low-grade inflammation in PCOS patients. Inflammation emerges as a response of the immune system, aiming to protect the body from pathogens or tissue damage. However, when chronic inflammation becomes excessive or continues persistently, it can harm tissues and lead to various health issues.

The role of increased inflammation in PCOS women within the immune system has started to be better understood. The immune system is a network that regulates immune responses and fights against foreign substances or diseases. Abnormalities in the immune system in PCOS, particularly changes in levels of different cell types such as T cells, B cells, and natural killer (NK) cells, have been associated. Additionally, some studies indicate that autoimmune reactions (aggression against the body's own tissues) might be heightened in PCOS patients.

EFFECTS OF STEROID HORMONES ON THE IMMUNE SYSTEM

Sex steroids can influence the immune system through various mechanisms. These effects can be exerted by affecting immune cell counts and cytokine production (60). Androgens generally have anti-inflammatory effects. In cases of androgen deficiency, an increase in dendritic cell counts and receptor numbers in lymph nodes has been reported (61, 62). Additionally, they modulate the immune response by reducing pro-inflammatory T-lymphocyte ratios and increasing anti-inflammatory T-lymphocyte counts (63). However, androgens do not have a completely anti-inflammatory effect on the immune system. PCOS patients with hyperandrogenism and androgen-induced mice have been found to have higher macrophage counts in ovarian tissue (64).

Understanding the effects of estrogen on the immune system is more complex. Since estrogen levels vary throughout the menstrual cycle, its effects are intricate (65, 66). Estrogen levels peak during the ovulatory phase and can negatively influence pro-inflammatory effects. In the early follicular phase when estrogen levels are lower, it may contribute to pro-inflammatory effects (67). Estrogen has been shown to be involved in macrophage activation through the alpha receptor (66). Studies have demonstrated increased macrophage response to bacterial infections in women with high estrogen levels (66).

PCOS AND IMMUNE SYSTEM CELLS

Macrophages are anti-infective cells and play a role as antigen-presenting cells (APCs) in cellular immunity. Increased macrophages and pro-inflammatory cytokines in adipose tissue in PCOS patients lead to insulin resistance (4,5). Insulin resistance is one of the most important etiological factors in PCOS. Elevated insulin levels contribute to hyperandrogenism by increasing androgen production from theca cells. Additionally, they enhance chronic inflammation and insulin resistance in the ovaries by reducing insulin receptor auto-phosphorylation in granulosa cells. All of these factors contribute to the worsening of PCOS (6-8). Chronic inflammation is implicated as the cause of ovarian dysfunction in women with PCOS. Macrophages contribute to this inflammation by secreting various inflammatory cytokines (IL-6, IL-10, IL-18, MIF, TNF-a) (9). In an experiment conducted on mice, the ratio of anti-inflammatory M2 macrophages decreased while the ratio of pro-inflammatory M1 macrophages increased in DHEA-S-induced subjects. This finding supports the impact of hyperandrogenism on inflammatory processes in women with PCOS (10). Studies have demonstrated an increase in neutrophil counts and an elevated neutrophil-to-lymphocyte ratio in PCOS patients (11,12). This serves as evidence of low-grade inflammation.

Dendritic cells function as antigen-presenting cells in lymphoid tissues within the immune system, playing a crucial role in transporting antigens to lymphoid organs (13-15). Studies have revealed a decrease in dendritic cell counts and disruptions in related cytokines in PCOS patients. Research conducted on follicular fluids in the ovaries has

reported that the maturation of dendritic cells in this context is associated with gonadotropins and estrogen concentrations (16-22).

Natural killer (NK) cells are immune system lymphocytes that play a significant role in innate immunity due to their cytotoxic effects. They regulate their activation and functions through immunoglobulin-like receptors on their surfaces and HLA-1 ligands. It is believed that immunoglobulin-like receptors and HLA-1 ligands are associated with PCOS development (23). Additionally, in PCOS-inflicted infertile women, lower levels of NK cells and disrupted cytokine networks have been detected in the secretory endometrium. These findings could hold predictive value for infertility in these patients (24,25).

T lymphocytes, also known as T cells, are fundamental cells in cellular immune responses. CD4 and CD28 T lymphocytes exhibit both pro-inflammatory and cytotoxic characteristics (26,27). These cells have been found to be higher in the peripheral blood samples of PCOS patients compared to normal women, and their potential association with long-term cardiovascular risks has been suggested (28). Additionally, in follicular fluids of PCOS-inflicted infertile women, the CD8 T lymphocyte ratio has been significantly lower compared to the CD4 T lymphocyte ratio (29). This finding implies that T lymphocyte dysfunction could be involved in the pathogenesis of PCOS.

T-regulatory (T-reg) cells are lymphocytes that play a role in regulating immune balance, allergic reactions, and tumor immunity. In PCOS patients, circulating levels of T-reg cells have been found to be lower due to decreased response to interleukin-2, which leads to reduced

levels (30). Th-17 cells, on the other hand, exhibit both pro-inflammatory properties and effects like neutrophil activation and chemotaxis. The Th-17/T-reg ratio reflects the balance within the immune system. Decreases in the T-reg/Th-17 ratio are associated with autoimmune and inflammatory diseases. A study indicated that this ratio is skewed towards Th-17 in PCOS and autoimmune thyroiditis patients (31). Nasri et al., based on their research, argued that an increase in Th-1 and Th-17, coupled with a decrease in T-reg and Th-2 cells, could potentially play a role in PCOS pathogenesis (32).

PCOS AND IMMUNE SYSTEM CYTOKINES

PCOS patients experience an increase in visceral fat accumulation. The adipocytes in the increased fat tissue undergo necrosis due to exposure to hypoxia, leading to the migration of inflammatory cells to the area. Abnormal levels of cytokines released by these inflammatory cells can lead to immune system imbalances.

Transforming growth factor β1 (TGF-β1) is a molecule that influences tissue fibrosis, embryo development, and endocrine metabolism. It has been associated with follicular formation, hyperandrogenism, and insulin resistance in PCOS patients (33,34). TGF-β1 can promote follicular growth, luteinization, and ovulation in granulosa cells. It achieves these effects by regulating Smad activation and phosphorylation (35,36). Periodic synthesis of ovarian hormones is essential for a healthy ovarian microenvironment. A key enzyme in the conversion of androgens to estrogens is aromatase, encoded by the CYP19 gene. Disruption of the expression of this gene leads to

hyperandrogenism due to aromatase deficiency. TGF-β1 has been shown to inhibit CYP19 gene expression in a dose- and time-dependent manner (37,38). The decrease in the conversion of androgens to estrogens results in hyperandrogenism, and the resulting low levels of estrogen concentration can lead to clinical features of PCOS such as follicular atresia, stromal fibrosis in the ovaries, hyperinsulinemia, and endometrial malignancy.

Growth differentiation factor 8 (GDF8) is a member of the TGF-β family. It negatively regulates the balanced development of human skeletal muscles. Recently, it has been considered a potential risk factor in individuals with insulin resistance (39). Compared to normal-weight PCOS patients, higher GDF8 concentrations have been found in the follicular fluid of obese PCOS patients. PCOS women with elevated GDF8 concentrations and low progesterone levels have been reported to have lower pregnancy rates (40). Furthermore, an increase in GDF8 concentrations has been associated with decreased LH levels, decreased estradiol levels, and a reduction in antral follicle count (41).

Secreted frizzled-related protein 4 (SFRP4) is a newly discovered adipokine that can inhibit the opening of calcium channels in islet cells, potentially disrupting insulin secretion (42). Bicer and colleagues have proposed that elevated SFRP4 levels could be associated with insulin resistance, ovarian follicle count, ovarian volume, and hyperandrogenism, suggesting that it might be an etiological factor in the pathophysiology of PCOS (43).

Leukemia inhibitory factor (LIF) expression in the endometrium is approximately 4-5 times higher during the mid and late secretory phases compared to the proliferative phase. In PCOS patients undergoing ovarian stimulation, it has been observed that LIF concentrations are inversely proportional to the LH/FSH ratio. The same study indicated that implantation rates in PCOS patients were significantly lower than in the control group, and low levels of LIF concentration in follicular fluid could potentially be associated with decreased implantation rates (44).

Epidermal growth factor (EGF) triggers cell proliferation in various tissues. EGF and its receptor are present in the endometrium, deciduous layer, blastocyst, follicular fluid, and other reproductive organs. Increased concentrations of EGF in PCOS patients are believed to lead to numerous small follicles and lower pregnancy rates in IVF treatments (45-47). Additionally, it has been shown that endometrial androgen receptor expression is inhibited by EGF and progesterone, while it is increased by estrogen and androgens (48)

PCOS AND AUTOIMMUNITY

Low progesterone levels in PCOS can lead to immune system stimulation and the formation of various autoantibodies (49). Hypothyroidism and PCOS share similar clinical features such as insulin resistance, obesity, and glucose metabolism disorders. Women with the coexistence of PCOS and autoimmune thyroiditis have higher body mass indexes and insulin resistance compared to only PCOS

patients (50). A study has demonstrated that thyroid peroxidase antibody (TPO-Ab) concentrations affect ovarian reserve (51).

Anti-ovarian antibodies (AOAb) can lead to granulosa cell degeneration, disturbances in steroid metabolism within ovarian cells, issues in follicular development, and alterations in progesterone and estrogen levels. Studies have shown that the detection rate of AOAb in women with premature ovarian insufficiency and early menopause ranges from 50% to 70% (52,53). Additionally, histological findings of PCOS patients have been associated with autoimmune oophoritis (54).

Antinuclear antibodies (ANA) are autoantibodies produced in the nucleus that target DNA, RNA, and molecular complexes, and they have been associated with several autoimmune diseases (55-59). In a study, Samsami et al. reported higher levels of ANA in PCOS patients, with the most common subtype being SS-A (2). Rashid and colleagues found that ANA in PCOS patients is associated with hyperandrogenism and serum glucose concentrations, but it did not affect other hormonal parameters (1).

RESULT

In conclusion, the relationship between PCOS and the immune system is quite complex and multifaceted. Inflammatory processes in women with PCOS have become a frequently emphasized topic in recent times. The significance of the immune system in PCOS and its role in the pathophysiology have been elucidated by numerous studies, with increasing levels of evidence emerging. Understanding the immunological aspect of PCOS will allow us to better evaluate the

clinical symptoms and long-term outcomes of the disease. The role of the immune system can help us approach processes such as hormonal imbalances, insulin resistance, and chronic inflammation from a broader perspective. Research conducted in this field will provide important data in the future regarding the clinical symptoms of PCOS and the long-term consequences that affect various organs and metabolic systems. However, despite the growing understanding of the effects of immune system components, there is insufficient data regarding their place in diagnosis and treatment, necessitating a need for advanced research in this field.

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CHAPTER V

POLYCYSTIC OVARY SYNDROME AND ENVIROMENTAL TOXINS

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1. Introduction

Polycystic ovarian syndrome is a reversible metabolic condition which contributes substantially to the global epidemic of lifestyle-related chronic illness. Polycystic ovary syndrome (PCOS), also called Stein-Leventhal syndrome, is the most common chronic endocrine disorder in women of reproductive age. (Escobar-Morreale, 2018, Franks, 1995).The name polycystic ovary syndrome describes the numerous small cysts (fluid-filled sacs) that form in the ovaries. follicles develop from primitive follicles, but in the early period of destruction of ovarian function, follicle development stops. (El Hayek et al., 2016, Goodarzi et al., 2011).

The diagnosis rate of PCOS is one in every 5 women of reproductive age. The basis of PCOS is the abundance of androgens. Hyperandrogenism is evidenced by high levels of free (unbound) testosterone in the blood, a hormone important to the pathophysiology of PCOS. Predisposing risk factors are genetics, neuroendocrine, lifestyle/environment and obesity. Some women have a higher risk of developing PCOS because they have dominant genes. Physical exercise, lifestyle, and diet are environmental factors that vary greatly by population when examined. Endocrine disrupting chemicals and glycotoxins are also environmental factors.(Kshetrimayum, C.,et all,2019)

This factors may cause genetic variance and disruption of the metabolic and reproductive pathways. This leads to PCOS phenotypes and related complications. Androgen exposure can affect the LH:FSH ratio, inhibiting the hormone levels of GnRH to increase high pulse

rate, leading to follicular arrest and dysplasia. These factors cause hyperinsulinemia, hyperandrogenism, oxidative stress, irregular menstrual periods. All these causes result in metabolic syndrome. (Figüre 1.) (Walters et al., 2018, Barber et al., 2016, Rojas et al., 2014)

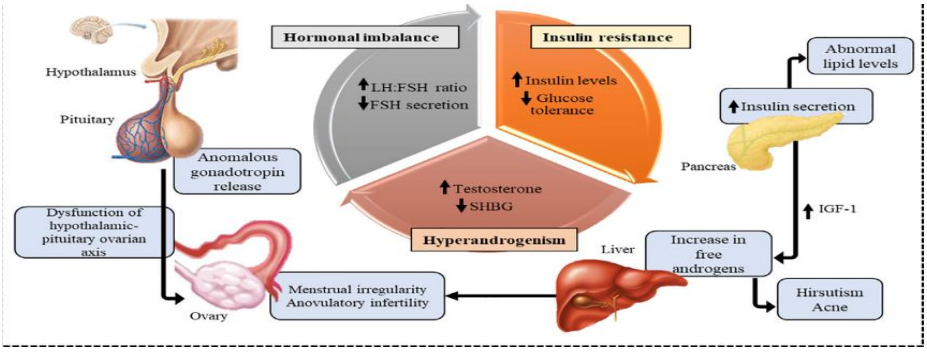

Figure 1. PCOS pathogenesis. (Walters et al., 2018).

The pathophysiology of this endocrinopathy is still unknown, but the heterogeneity of its characteristics suggests that environmental and lifestyle factors, as well as genetic factors, are of scientific and clinical relevance. People's health is affected by plasticisers such as bisphenol A (BPA) or phthalates and advanced glycation end products (AGEs). Since it can lead to undesirable health consequences in women's life, more care should be taken against such exposures. (Koch, C. A., et all 2015).

Clinical and/or biochemical hyperandrogenism, ovulatory dysfunction and suggests that the ovary is vulnerable to elevated amounts of BPA. BPA has the ability to bind to both subtypes of nuclear estrogen receptor, ERα and ERβ, due to its chemical structure similar to synthetic estrogen diethylstilbestrol. Therefore, BPA is considered to be a xenoestrogen that mimics estrogen and shows hormone-like

properties. BPA may affect the female reproductive tract through modifying ovarian steroidogenesis, folliculogenesis, and morphology of ovaries. (Kupier.., et all 1998)

Enviromental Toxins

Environmental toxins known to have an effect can be inhaled, removed from the skin and mucous membranes can be absorbed or swallowed. The possible environmental risk is important to consider factors involved. The general population is also exposed to pollutants such as tobacco smoke, lead, pesticides and mercury. In 1996, a mandate under the Food Quality Protection System and the Safe Drinking Water System was given to the United States Environmental Protection Agency (US EPA). As a result of studies, EDCs have been shown to impair male reproductive health, impair sperm quality and cause cryptorchidism. (Colborn ,1994, Food Quality Protection Act of ,1996)

With the industrialized food system toxic chemicals are used more frequently and impair reproductive health and cause PCOS development. Since agents such as starch-based and dairy foods contain too much toxic substances, ınsulinogenic effects increase and contribute to the formation of PCOS. Low consumption of starch-based foods and dairy products obesity and insulin resistance are reduced, which also leads to a reduction of hyperandrogenism in women with PCOS. More extensive studies should be conducted to identify environmental toxins. EDCs are an important element of this process. (Rojas et al., 2014).

Endocrine Disrupting Chemicals

Endocrine disrupters (EDs), as defined by the World Health Organisation (WHO), are substances that cause adverse health effects in a healthy organism or its future generation, or a (sub-)exogenous substance or a substance that causes adverse health effects in the population, known as "mixtures". The compounds that are classified as EDCs are a wide range of compounds with different chemical structures - it is a heterogeneous group. As natural and synthetic endocrine disrupting compounds.(Diamanti-Kandarakis et all..,2009)

They are divided into 2 separate groups.

Table 1. Endocrine Discrupting Chemicals

Natural EDC	**Synthetic EDC**
•Phytoestrogens (cumestrol, genistein, etc.) • Mycoestrogens (Zeralenon et al.)	•Plasticizers (Bisphenol A, phthalates), •Pesticides (Chlorpyrifos, methoxychlor), •Fungicides (Vinclozolin), •Pharmaceutical substances (Cimetidine, Diethylstilbestrol) • Industrial by-products (Perchlorate, dioxin)

Table1.: EDC classification

When their mechanisms of action are examined, EDCs act by mimicking endogenous hormones. Many vital functions such as homeostasis, reproduction, development in the womb interact with nuclear receptors in function. ERα, ERβ and androgen receptors (AR),

pregnan X receptor (PXR), thyroid hormone receptor (THR), retinoid X receptor (RXR) and peroxisome proliferator – activated receptor alpha and gamma (PPARa and PPARγ), nuclear aryl hydrocarbon receptor EBK interacting are examples of receptors. Membrane estrogen receptors, non-steroidal neurotransmitter. Among the receptors, serotonin, dopamine, norepinephrine receptors also interact with IBCs. are structures. The impact of EDCs mechanisms are shown in figure 2. (Lovekamp-Swan, T., et all 2003)

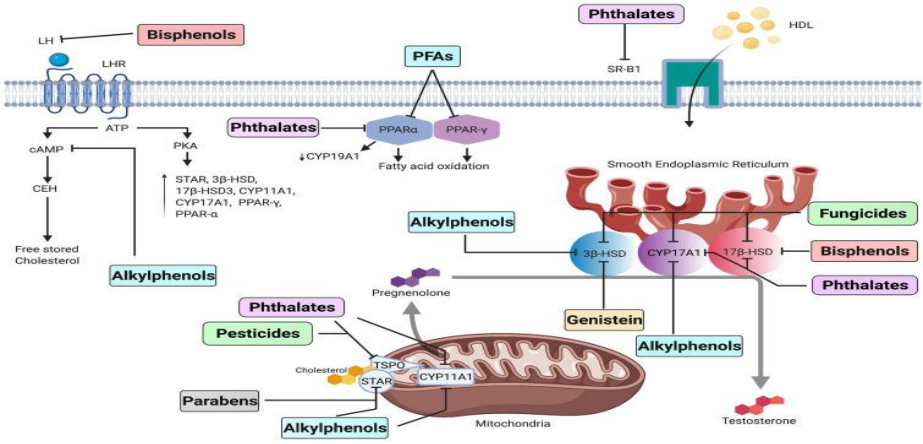

Figure 2. Mechanisms of EDC

Concern for EDCs is increasing worldwide. Also some people as a result of exposure to the information that they cause reproductive and hormonal diseases such as breast-prostate cancers (BPA), endometriosis (Dioxin,PCBs), infertility (phthalates, estrogens, pesticides), diabetes/metabolic syndrome (BPA), precocious puberty (estrogens, BPA), obesity (BPA, tributyl tin, organochlorine pesticides). The effect of BPA, one of the endocrine disrupting

chemicals, on the pathogenesis of PCOS has been the subject of many studies in the literature. Studies have accelerated in recent years. The effects of BPA on insulin signalling, fat metabolism, steroidogenesis steroidogenesis and HPO axis have been investigated in studies. (Mukhopadhyay, R.,et all ,2022)

One of the possible risk factors for PCOS is that it is observed in human cell line studies in vitro caused one. BPA mimics 17-β estradiol activity, HPO Deterioration of the steroid feedback mechanisms in the axis and the effect of steroids in the ovaries is general. As a result, it suppresses HPO axis functions. In addition, circulating LH levels and disrupts the LH:FSH ratio. When all these are considered together, BPA is a factor in the pathogenesis of PCOS considered as an important risk factor.(Mikhael, S.,et all 2019)

Bisphenol A (BPA) was first discovered in 1981 by the Russian chemist Alexandr P. Dianin. synthesized many different products, especially the production of epoxy resins and polycarbonates. It is a synthetic chemical used in the industrial field. Bisphenol A has been found to bind to and activate the human oestrogen receptor and is therefore reported as a synthetic oestrogen.. It has a similar structure to diethylstilbestrol (DES) and estradiol. Since this situation creates an estrogen-like response, BPA is included in the EBK. (Gao, X., & Wang, H. S. ,2014).

has caused. Bisphenol A widely exists in food packing, suggests that the ovary is vulnerable to elevated amounts of BPA. BPA has the ability to bind to both subtypes of nuclear estrogen receptor, ERα and ERβ, due to its chemical structure similar to synthetic estrogen

diethylstilbestrol. Therefore, BPA is considered to be a xenoestrogen that mimics estrogen and shows hormone-like properties. BPA may affect the female reproductive tract through modifying ovarian steroidogenesis, folliculogenesis, and morphology of ovaries. Total serum BFA levels were found to be significantly higher in women with PCOS compared with controls in a study of women with and without PCOS. Furthermore, a significant relationship was found between BFA and high androgen concentrations. (Acconcia, F., et all,2015).

The increase in androgen level can be explained by different mechanisms. In rat studies, the increase in GnRH/LH pulse frequency and BFA acting as a strong ligand of SHBG by changing the androgen metabolism in the liver, thus increasing the amount of free androgens by replacing androgens can be counted among the mechanisms. . Significantly higher serum concentrations of BFA were found in obese women compared to non-obese women with PCOS. In the same study, it was determined that high serum BFA levels were significantly associated with total and free testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEAS) levels. These results suggest that BFA may increase androgen concentration in adult women. (Polak..,et all 2020).

Advanced Glycation End Products

Advanced glycation end products (AGEs), also developed as glycotoxins, are proinflammatory molecules derived from glycotoxins. In fact, glycotoxins may decrease adipocyte glucose uptake and alter glucose metabolism transport in human cells. Inflammation caused by

AGE can also lead to reduced insulin sensitivity. It is also known that obesity itself worsens IR (insulin resistance). Central and visceral obesity is present in approximately 30-75% of women with PCOS. A positive correlation between serum levels of glycotoxins and the waist-hip ratio has been reported, and in has been reported and in vitro studies support the role of AGEs in the stimulation of adipogenesis. Insulin sensitivity may also be reduced by AGE-induced inflammation . In addition, obesity is associated with lower levels of soluble RAGE, which reduces the clearance of AGEs and promotes their deposition in reproductive tissues, such as the ovary, where they can interfere with steroidogenesis.

All AGEs, despite the type of exposure It interacts with cell receptors called RAGE (RAGE receptor). AGEs have the function of trigger signal transduction receptors. It plays a role in ageing, diabetes, atherosclerosis, female fertility and in the development of several types of cancer.. Using the ERK1/MAPK signaling pathway, AGEs have also been found to interfere with oocyte development, duration and maturation in preovulatory follicles.(Mouanness, M., Merhi, Z. 2022).

Summary

EDCs and AGEs have an important place among toxic substances with the increase of western diet and lifestyle. It is frequently involved in the pathogenesis of PCOS. Data obtained from scientific studies conducted in recent years, confirmed their negative role in its pathophysiology. PCOS and its adverse epigenetic effects (summarized below) (Figure 3) . Exposure to these toxic substances, which form the basis of the health

problems of future generations, should be prevented.(Rutkowska, Fertil Steril ,2016.)

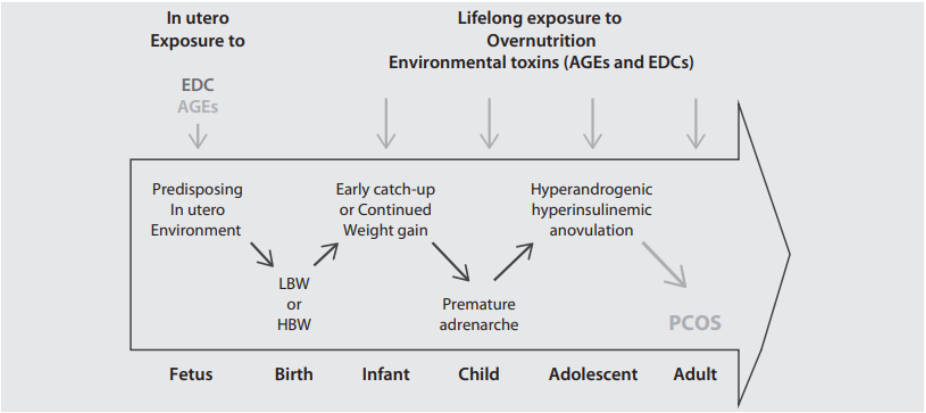

Figure 3.environmental toxins and effects

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CHAPTER VI

POLYCYSTIC OVARY SYNDROME AND MECHANISMS OF INSULIN RESISTANCE

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1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine pathologies in women of reproductive age. The rate of PCOS occurrence is 6–10% in women of reproductive age and the prevalence rate is double[1–3]. PCOS is characterized by hyperandrogenism, polycystic ovarian morphology, and dysfunctional ovulation, as well as metabolic abnormalities such as insulin resistance (IR) and obesity.

A recent study showed that the most important chronic disorders associated with PCOS are metabolic disorders, obesity and type 2 diabetes mellitus (T2DM) [4). Furthermore, studies have shown that worsening of IR over time in obese PCOS women is a risk factor for the early development of T2DM(5).The underlying pathogenesis of PCOS still remains unclear. Recent studies have suggested that genetics, epigenetic changes, oxidative stress, environmental factors, mitochondrial dysfunction, chronic low-grade inflammation, and metabolic disorders are involved in the development of PCOS, thus impairing normal ovarian function [6–13].IR and compensatory hyperinsulinaemia (HI) are major factors of PCOS pathophysiology. They are involved in the development of hyperandrogenaemia and reproductive dysfunction by various mechanisms[14].

At the moment, there are four widely known phenotypes of PCOS: type A, polycystic ovary (PCO), chronic oligo-anovulation (OA) and hyperandrogenism (HA); type B, OA and HA; type C, PCO and HA; and type D, PCO and OA [15]. IR is present in all phenotypes, and

insulin sensitivity shows diffences according to the PCOS phenotype. IR is most common in the classical phenotype (Types A and B) (80%), followed by ovulating PCOS (65%) and non-hyperandrogenaemic PCOS (38%) [16]. In order to determine how to treat this multifaceted syndrome, a comprehensive understanding of the pathophysiology of PCOS and its relationship with reproductive/metabolic disorders is required.

2. Insulin Resistance in PCOS

IR indicates the increased amount of insulin required to perform metabolic action. Insulin is needed for mitogenic and reproductive functions as well as metabolic activities [17]. The rapid and fast glucose analysis help to detect IR. Therefore, homeostatic model assessment has been established and used in clinical research as well as metabolic investigations in PCOS [17-20].

The studies showed that diagnostic criteria of IR have limited impact on IR detection in PCOS. In previous studies, it was found that large population of PCOS women is suffering from compromised glucose tolerance and T2DM [21,22]. According to various studies, it was found that all those PCOS females who are obese and overweight are at greater risk of the disturbances in glucose metabolism. These patients are required to check their glucose regularly with proper metabolic profiling [22–28].

3. Pathways of Insulin Resistivity in Patients with PCOS

Genetics and Fetal Origin

PCOS is an autosomal dominant genetic disease with various expression patterns which begins in early life, and metabolic changes precede reproductive abnormalities. Cluster analysis of nearly 1000 women with PCOS identified the metabolic subtype of PCOS. It is characterized by lower levels of LH and SHBG and higher BMI, glucose and insulin levels [32].Twin and family cluster studies have proposed HI has a genetic component in PCOS. These studies also suggested a family history of T2DM is associated with significant insulin secretion defects [30,31]. The daughters of women with PCOS develop HI and lower adiponectin levels before puberty [32], which persist throughout adolescence [33].

PCOS is associated with specific gene mutations. These mutations are involved in regulating sheath steroid production, follicular maturation, or insulin signalling through the modified proteins they encode, such as insulin receptors, LH/HCG receptor activators, cell traffic proteins, and transcription factors [34, 35].

A meta-analysis stated that the Gly972Arg polymorphism in insulin receptor substrate 1 (IRS-1) mediates the pathogenesis of PCOS by increasing fasting glucose levels and is a risk factor for susceptibility to PCOS [36, 37]. But, the genetic assessment of insulin-related genes is affected by the diagnostic criteria and genotyping methods employed with patients, effecting the results[38]. Exposure to adverse intrauterine

environments can lead to varying degrees of IR and HI. Exposure to dihydrotestosterone and insulin in the second trimester of pregnancy produces a PCOS-like phenotype and increases the risk of abortion [39]. Intrauterine growth restriction can affect fetal insulin secretion, and IR trends in PCOS may be involved in develop- mental origin and preprogramming as a nutritional compensation mechanism [40, 41]. Adolescents with a history of low birth weight are more likely than normal women to have high androgen levels and PCOS-like manifestations of IR [42, 43].

Insulin signal transduction pathway

Insulin is a small peptide receptor-binding hormone released by pancreatic beta cells. Insulin has two main signalling pathways: metabolism and mitosis. Metabolism is mediated primarily by phosphatylinositol 3-kinase (PI3-K) and the serine/threonine kinase Akt/protein kinase B (PKB), also known as the PI3-K pathway. Through these pathways, insulin enables the translocation of glucose transporter 4 (GLUT4) from intracellular vesicles to the cell surface and stimulates glucose uptake [44] and then leads to the inactivation of serine phosphorylation of glycogen synthase kinase 3 (GSK3), increasing glycogen, protein, and fatty acid synthesis. It also activates mammalian target of rapamycin (mTOR) to regulate protein synthesis and degradation [44]. The mitotic pathway is the mitogen-activated protein kinase- extracellular signal-regulated kinase (MAPK-ERK) pathway, which is activated by insulin receptor-mediated phosphorylation of Shc or IRS. This progressively stimulates the translocation of cascade erk1/2 to the nucleus and phosphorylates

transcription factors to stimulate cell growth and differentiation and regulate gene expression [45, 46]. Increased serine phosphorylation and decreased tyrosine phosphorylation of insulin receptors and IRS can terminate insulin action, resulting in post-binding defects in insulin signal transduction and leading to insulin dysfunction in women with PCOS [47, 48].

4. Effects of Polycystıc Ovary Syndrome and Insulın Resıstance on Uterus and Ovarıes

Ovarian androgen overload is the essence of PCOS. HI enhances intrathecal steroid production and leads to damaged follicular maturation. Insulin receptors are generally distributed in stromal and follicular ovarian cells. There is direct ovarian effect of insulin on steroid production and the ovulation control [49,50]. Under physiological circumstances, insulin acts as a helper gonadotropin through its homologous receptor LH induces luteinization in granulosa cells [51]. HI can lead to androgen-dependent anovulation via various mechanisms. Membrane cells are the major site of androgen production in the ovaries. Insulin acts on the membrane cells of the ovary to directly trigger androgen synthesis by increasing the activity of cytochrome P450c17α, a key enzyme that regulates androgen biosynthesis encoded by CYP17.

In anovulatory PCOS, the synergistic effect of high insulin and LH levels may induce premature expression of LH receptors in small follicular subsets. In this case, granulosa cells differentiate prematurely and follicular growth comes to a halt [52]. The effect of insulin on

glucose metabolism was significantly reduced in granular lutein cells of ovaries with typical PCOS phenotypes, while the effect of insulin on steroid production was unaffected [52].

PCOS have shown that IR and HI affect endometrial physiology negatively. Endometrium express molecules involved in insulin signalling pathways. Endometrial expression of insulin receptors, AS160, IRS proteins, PKC, and GLUT4 in the women with PCOS is damaged and associated with adverse reproductive outcomes [39]. Hyperinsulinaemia can damage decidualization of endometrial stromal cells in vitro through the transcriptional inhibition of FOXO-1 [53]. The insulin sensitizer metformin promotes GLUT4 transcription by increasing AMPK, improves IR, and therefore indirectly restores endometrial function in PCOS patients [54].

5. Diagnosis and Evaluation of IR in PCOS

The 'gold standard' technique for assessing metabolic IR in vivo is the Glucose clamp technique. The amount of glucose injected was equal to the amount of glucose absorbed by the peripheral tissue, which can be used to measure peripheral sensitivity to insulin [55]. Minimal model analysis using a frequently sampled intravenous glucose tolerance test (FSIGT) is an alternative to the simplified clamp procedure for assessing insulin secretion in insulin sensitivity experiments [56]. However, both these tests are complex, expensive and time-consuming procedures that are unfit for clinical practice. Recently, clinical practice has developed many simple, effective and cheap alternative quantitative indicators, such as waist circumference, wrist circumference waist-to-

hip ratio, BMI, [57] and other anthropometric markers; fasting insulin, oral glucose tolerance test (OGTT), homoeostasis model assessment of insulin resistance (HOMA-IR), glucose/insulin ratio (G/I), lipid/lipoprotein ratio, quantitative insulin sensitivity test index (QUICKI) and other biomarkers [58–61].

These indices are reasonably correlated with each other and with the gold standard clamp technique. Currently the best and most widely validated marker is HOMA-IR, but the cut-off point for the diagnosis of PCOS-IR is still not universally accepted [62]. Studies points that a more complex evaluation of the decrease in insulin sensitivity as a continuous variable is required in clinical practice [10]. Morover, because of the strong association between inflammation and IR, interleukin-6 (IL-6) [63] and ferritin [64] are becoming increasingly popular in the evaluation of IR, while cytokines such as leptin [65] and adiponectin [66] have also been proposed as new IR markers. However, conflicting data limit their use in clinical practice , and much more work is needed to determine the relevance of IR markers in women with PCOS [67]

6. Treatment Options for Insulin Resistance, and PCOS

Lifestyle Change

Recent studies recommend that women with PCOS and reduced insulin sensitivity should make lifestyle changes. They should start insulin sensitivity treatment, even with no significant change in glucose tolerance. The first step in managing IR is lifestyle change, which is the

core of improving multiple metabolic and endocrine disorders in women with PCOS [68]. Diets with calorie-restriction may be the best option for reducing IR [69]. Mediterranean diet— which contains a high intake of vegetables, fruits, legumes, sea- food, nuts, whole grains, vegetable oils—combined with a low-carbohydrate regimen improves endocrine disorders and menstrual cycles in patients with PCOS [70]. International evidence-based guidelines recommend that all women with PCOS, especially those who are overweight or obese, should exercise for at least 150 minutes, 90 minutes of which should be vigorous exercise [71]. But it should be remembered that treatment of PCOS is a long-term process. It requires high self-discipline in physical exercise and diet and prone to relapse.

Insulin Sensitization Therapy

Metformin

Metformin, PCOS için 'en yaygın' olarak kullanılan insülin duyarlılaştırıcıdır. It reduces hepatic glucose production, improves peripheral tissue sensitivity to insulin, inhibits gluconeogenesis and adipogenesis, and prevents excessive insulin activity in the ovary [72]. Studies have shown that metformin not only reduces weight and metabolic disorders but also corrects menstrual cycles, restores ovulation, and even increases chances of pregnancy [73]. Guidelines recommend the use of metformin in insulin-resistant women with PCOS and obesity to manage endocrine and metabolic disorders, in conjunction with lifestyle changes (74, 75]. Metformin improves insulin sensitivity by increasing the translocation of the ‘glucose

transporters' GLUT1 and GLUT4 to cell membranes [76], activating the AMPK signalling pathway [77].

Thiazolidinediones

Thiazolidinediones (TZDs) are alternative drug therapy for PCOS-related metabolic and reproductive abnormalities in women who respond poorly or cannot tolerate metformin[78,79]. TZDs and 'peroxisome proliferator activated' receptor γ (PPAR-γ) agonists are real insulin sensitizers. TZDs are effective for IR and HI in both obese and lean women with PCOS. They are also effective in improving hyperandrogenaemia, abnormal glucose tolerance, and ovulation disorders in women with PCOS. Moreover, the combination of metformin and TZDs has a synergistic effect with greater improvement in IR and menstrual frequency in PCOS than metformin alone [80].

New Antidiabetic Drugs

Current studies have shown that Glucagon-like peptide-1 analogues (GLP-1RAs) has excellent therapeutic effects in improving hyperandrogenaemia and menstrual frequency, reducing manifestations of metabolic disorders and long-term cardiovascular risk in obese women with PCOS [81,82].

Sodium-glucose cotransporter type 1 and type 2 inhibitors (SGLT1/2is) play important roles in glucose homoeostasis by reducing HI and improving IR by acting on glucose absorption[83]. The mechanism of action of SGLT1/2is in PCOS has not been fully understood. But weight loss and HI, improved IR and glucose metabolism, and

cardioprotective effects are beneficial in PCOS, suggesting that SGLT1/2is may be a novel treatment option [84-86].

Natural Molecules and Dietary Supplements

Several studies have shown that inositol has excellent insulin sensitization efficiency in women with PCOS and helps ovulation [87]. It improves the health of tissues, while long-term high-dose DCI monotherapy has a negative impact [88]. Therefore, inositol therapy should be tailored to the specific needs of patients.

Alpha-lipoic acid [89] and 'omega-3' fatty acids are supplements that improve lipid and insulin sensitivity through their anti-inflammatory and antioxidant properties.[90]. Studies show that coenzyme Q10 has beneficial effects on glucose and lipid metabolism, HOMA-IR, insülin and total testosterone levels in PCOS and also improves ovarian function [91–93]. Vitamin E combined with coenzyme Q10 can improve IR and serum SHBG levels [94, 95]. Supplementation with probiotics, prebiotics, and synbiotics in PCOS can improve IR, regulate the immune system, lipid profile, other metabolic disorders and protect the intestinal barrier [96, 97].

7. Conclusion

In general, women with PCOS develop IR owing to abnormal insulin signalling and metabolic dysfunction. The pathogenesis of IR in PCOS is not clear. It includes genetic and epigenetic changes, deficiency of insulin signal transduction, obesity, hyperandrogenaemia, and inflammation. IR in different PCOS tissues can selectively affect

metabolic or mitotic pathways, including the ovaries. Therefore, effective prevention and treatment options should be evaluated to improve IR in PCOS patients. Lifestyle changes and insulin sensitization therapy can be effective for improving insulin sensitivity and ovulation and reducing androgen levels. PCOS'ta insülin duyarlılaştırıcısı olarak en yaygın 'Metformin' kullanılır. However, it should be remembered that all the medications mentioned for PCOS are still off-label and more well-designed prospective studies are needed to evaluate these treatments in terms of efficacy and futility.

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CHAPTER VII

PCOS AND INFLAMMATION

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1.OVERVIEW

Polycystic ovary syndrome (PCOS) is very common disease and anovulation, hyperandrogenism and radiological findings of cysts in the ovary are characteristic symptoms. (Hachey, Kroger-Jarvis, Pavlik-Maus, & Leach, 2020) PCOS provoke the systemic diseases like obesity and insulin resistance. (Abraham Gnanadass, Divakar Prabhu, & Valsala Gopalakrishnan, 2021) (Caserta et al., 2014) PCOS is considered a chronic low grade inflammatory disorder. (Ambeba, 2013) Endothelial cell disorders may be caused by inflammatory cytokines and produce of inflammatory cytokines elevated in patients with PCOS. (Ewa Rudnicka et al., 2021) Cytokines are synthesised by the various types of immune cells which have a specific impact on other cells. (Sirotkin, 2011; Zhang & An, 2007) In the ovary, cytokins secreted by oocytes, follicular cells and leukocytes and they can function both paracrine and autocrine. (Qiao & Feng, 2011; Richards & Pangas, 2010; van der Spuy & Dyer, 2004)

PCOS women have elevated levels of CRP, TNF-α, interleukin 18, interleukin 6, ferritin and transferrin. (Patel, 2018; E Rudnicka et al., 2020; Xiong, Liang, Yang, Li, & Wei, 2011) Also elevated levels of white blood cells, plasminogen activator inhibitör-1 (PAI1) detected in patients with PCOS. Natural killer cells (a type of lymphocyte) are also detected at increased levels in patients with PCOS. (He et al., 2020; Shojaei et al., 2022) Omentin and adiponectin are anti-inflammatory cytokins and as expected patients with PCOS have lower serum levels. (Franik et al., 2020; Ewa Rudnicka et al., 2021)

In order for the ovary to function properly, it is important that the levels of inflammatory markers are in balance. Imbalance between these markers causes ovarian dysfunction, which in turn leads to disruptions in steroid synthesis and follicular maturation. (Vural, Değirmencioğlu, Saral, & Akgül, 2010) This situation is schematized in figure 1.

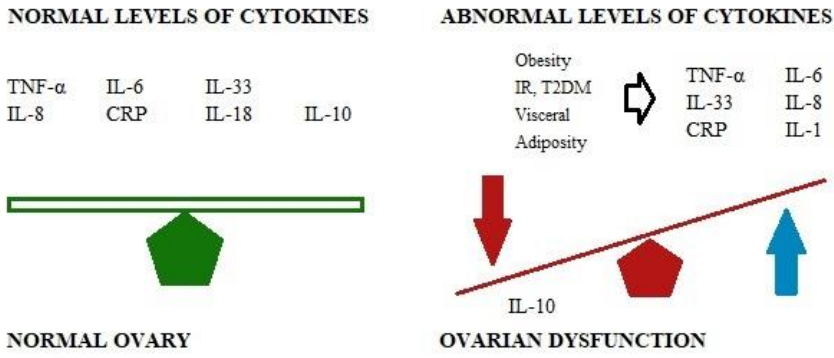

Figure 1. Effects of inflammatory markers in the pathogenesis of PCOS. (Abraham Gnanadass et al., 2021; Ewa Rudnicka et al., 2021)

2. INFLAMMATORY MARKERS

2.1. TNF-α

Tumor necrosis factor-alpha (TNF-α) is glycoprotein andproduced by neutrophils, activated macrophages, fibroblasts and endothelial cells in ovaries. (Abraham Gnanadass et al., 2021; Vassalli, 1992) TNF-α disrupts follicular maturation by causing irregularities in steroid hormone synthesis. (Abraham Gnanadass et al., 2021; Adashi, Resnick, Packman, Hurwitz, & Payne, 1990; Bilgin et al., 2020) In patients with

hyperandrogenism, serum TNF-α levels may be elevated and this may be a marker for metabolic syndrome risk. (Choi et al., 2012)

2.2. IL-6

Interleukin-6 is a cytokine that promotes the development of inflammation. IL-6 production increases at chronic inflammation, autoimmune disorders and PCOS as well. (Ewa Rudnicka et al., 2021; Yao et al., 2014) IL-6 produced by fibroblasts, white blood cells, granulosa cells of the ovary. These elevated levels in PCOS could be associated with insülin resistance. Detection of elevated IL-6 levels in OHSS patients indicates that IL 6 contributes to ovarian dysfunction. (Abramov et al., 1996; Wei et al., 2013)

2.3. IL-8

Interleukin 8 activates immune cells in inflammation. (Bickel, 1993; Bilgin et al., 2020) It plays an important role of oocyte development. (Arici et al., 1996) As expected IL-8 serum levels higher in PCOS patients. (Shah et al., 2019) There are few studies on PCOS and IL-8 interaction so more research needed for fully understanding effects of IL-8 in ovarian functions. (Ravishankar Ram, Sundararaman, Mahadevan, & Malathi, 2005)

2.4. IL-10

Interleukin 10 is an anti-inflammatory cytokine.PCOS patients have lower serum levels and considering inflammatory processes, this supports the current picture. (Chugh et al., 2021; Sylus, Nandeesha, & Chitra, 2020)

2.5. IL-18, IL-33, Macrophage İnflammatory Protein-1α, Monocyte Chemoattractant Protein-1

Interleukin-18 is a one of the cytokines and have a very strong role in the adaptive immune system. (Dinarello, Novick, Kim, & Kaplanski, 2013) IL-8 plays an active role in inflammatory processes in metabolic syndrome and insulin resistance. (Lee & Pratley, 2005) However, although insulin resistance and obesity are not present, IL-8 levels are elevated in PCOS patients. (Kaya, Pabuccu, Berker, & Satıroglu, 2010; Vettor, Milan, Rossato, & Federspil, 2005)

Interleukin-33 is a inflammatory molecule from the IL-1 family. (Schmitz et al., 2005) IL-33 helps regulate innate immunity and Th2 cell. In PCOS patients IL-33 contribute androgen synthesis. (Abraham Gnanadass et al., 2021)

Patient with PCOS have elevated serum MCP-1 levels. Increased concentrations of MIP-1α are also observed in PCOS. Both MCP-1α and MIP-1α (CCL3) are chemotactic chemokines secreted by macrophages and their stem cell inhibition is a remarkable effect in the inflammatory process. (Orostica et al., 2016)

2.6. Omentin-1

Omentin-1 is a glucoprotein and one of the members of adiponectin family. (Çelik, Nar, Nar, Sökmen, & Günver, 2021) It has anti-inflammatory effect. Serum omentin-1 levels are negatively correlated with obesity and insulin resistance. (Çelik et al., 2021) As expected

omentin-1 levels are low in the polycystic ovarian syndrome patients. (Franik et al., 2020; Tang et al., 2017)

2.7. CRP

CRP (C-reactive protein) is an acute phase protein. IL-6 and TNF-α activate the production of C-reactive protein. (Khatir et al., 2015; Ewa Rudnicka et al., 2021)In many studies, high CRP levels were found in PCOS patients regardless of body mass index and age. (Ewa Rudnicka et al., 2021) CRP elevation is positively correlated with fatty mass and insulin resistance. More studies are needed to clarify whether elevated CRP concentrations in patients with PCOS is cause or consequence of the inflammatory process.

2.8. Oxidative Stress and Advanced Glycation End Products

Advanced glycation end products (AGEs) is metabolically active proteins or lipids originated from interaction of reducing glucose on lipids and proteins. (Ewa Rudnicka et al., 2021; Sergi, Boulestin, Campbell, & Williams, 2021). This reactive substances cause an increase in androgen synthesis by negatively affecting the functions of granulosa and theca cells. AGEs and reactive oxygen species (ROS) serum levels positively correlated. Reactive oxygen species causes intracellular oxidative stress. In PCOS, AGEs and ROS markers have been shown as elevated, which lead to an assumption that ROS can participate in PCOS pathophysiology. (Murri, Luque-Ramírez, Insenser, Ojeda-Ojeda, & Escobar-Morreale, 2013)

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CHAPTER VIII

POLYCYSTIC OVARY SYNDROME (PCOS) AND ADOLESCENCE

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Polycystic Ovary Syndrome (PCOS) and Adolescence

Polycystic ovary syndrome (PCOS) ranks among the prevalent endocrine disorders affecting women in their reproductive years. Polycystic ovary syndrome (PCOS), initially characterized by Stein and Leventhal in 1935, is a multifaceted disorder characterized by persistent anovulation resulting from hyperandrogenism, amenorrhea, or oligomenorrhea. (Stein & Leventhal, 1935). It is approximated to impact between 5% to 10% of women in the age group of reproductive years. (Ehrmann, 2005). In clinical terms, it manifests with a spectrum of various symptoms:

- Cutaneous hyperandrogenism signs (hirsutism, acne)
- Menstrual irregularity (oligo- or amenorrhea, or irregular bleeding)
- Ultrasonographic polycystic ovaries finding (one or both)
- Obesity and insulin resistance

Due to the wide variation in clinical presentations, not all individuals with PCOS will exhibit all of these symptoms, making the diagnosis of PCOS challenging at times. Being diagnosed with PCOS carries lifelong implications, including an elevated risk of developing conditions such as metabolic syndrome, type 2 diabetes, obstructive sleep apnea, endometrial hyperplasia, and, potentially, cardiovascular disease and endometrial cancer(Barry, Azizia, & Hardiman, 2014; Carmina & Lobo, 2018; Nandalike et al., 2011).

During the last 25 years, globally recognized diagnostic standards have been established for adults, using different combinations of

unexplained hyperandrogenism, anovulation, and polycystic ovaries as outlined in the Rotterdam consensus criteria(Azziz et al., 2009; Fr & Tarlatzis, 2004) but the criteria used for diagnosing PCOS in adult women have posed challenges when applied to girls in the mid to late stages of puberty, and this is due to several reasons. First, irregular menstrual cycles and anovulation are common in normal adolescents. Second, the typical signs of hyperandrogenism in adults are less dependable in adolescents due to the transitional nature of hirsutism and the prevalence of acne vulgaris during this developmental phase. Third, measuring testosterone levels in adolescents is problematic because they can fluctuate during anovulatory cycles, reliable reference values for androgen levels in adolescent females are lacking, and it's unclear how well adolescent hyperandrogenism predicts adult hyperandrogenism. Fourth, polycystic ovary morphology, as defined by adult criteria, is frequently observed in normal adolescents.

Three international expert conferences, representing various subspecialties, have issued guidelines for diagnosing PCOS in adolescents(Ibáñez et al., 2017; Teede et al., 2018; Witchel et al., 2015). These documents concur on the essential criteria: the presence of persistent, unexplained ovulatory dysfunction (as evidenced by menstrual irregularities, assessed against age-appropriate standards) and clinical and/or biochemical signs of androgen excess (hyperandrogenism), as summarized in Table 1(R. L. Rosenfield, 2020).

Table 1. International Diagnostic Criteria for Polycystic Ovary Syndrome in Adolescents(R. L. Rosenfield, 2020)

Otherwise unexplained combination of:
1. Abnormal menstrual pattern as evidence of ovulatory dysfunction
a. Abnormal for age or gynecologic age, and
b. Persistent symptoms for 1 to 2 years
2. Clinical and/or biochemical evidence of hyperandrogenism
a. Hirsutism, especially if moderate to severe, is clinical evidence of hyperandrogenism
b. Elevation of serum total or free testosterone by a specialty reference assay is biochemical evidence of hyperandrogenism

Etiology and pathophysiology

The exact cause of PCOS remains unclear. Extensive evidence indicates that it develops as a complex condition influenced by a combination of genetic and non-genetic factors, both during intrauterine and extrauterine periods(R. L. Rosenfield & Ehrmann, 2016). In most cases, functional ovarian hyperandrogenism is typically the primary cause of excess androgen production and can explain the main characteristics of the syndrome, which include hirsutism, anovulation, and polycystic ovaries(R. L. Rosenfield & Ehrmann, 2016).

Diagnostic evaluation

Polycystic ovary syndrome (PCOS) often becomes apparent during adolescence, primarily characterized by issues with ovulation and excess androgens, known as hyperandrogenism. The syndrome presents clinical and biochemical heterogeneity. A PCOS diagnosis carries lifelong consequences, including a heightened risk of metabolic

syndrome, type 2 diabetes mellitus, and potentially cardiovascular disease and endometrial cancer. PCOS should be taken into consideration when evaluating adolescent females who complain of hirsutism, acne that doesn't respond to treatment, irregular menstrual cycles, acanthosis nigricans, and/or obesity as their primary concerns.

For adolescent females with one or more of the following traits, it is advisable to undergo an assessment for PCOS:

- An unusual level of hirsutism or a condition akin to hirsutism, such as inflammatory acne vulgaris, which does not respond well to topical treatments or oral antibiotics.
- Localized areas of excessive sexual hair growth, referred to as focal hirsutism, warrant attention for PCOS if they are accompanied by menstrual irregularities.
- Menstrual irregularities, which include persistent amenorrhea (absence of menstruation), oligomenorrhea (infrequent menstruation), or excessive uterine bleeding, are indicative of a need for PCOS evaluation

The most reliable single test for hyperandrogenemia in postmenarcheal females is the persistent elevation of serum testosterone levels above the norms established for adults, as determined by a specialized reference laboratory(Ibáñez et al., 2017; Witchel et al., 2015).

If a trustworthy measurement of total testosterone is readily accessible, it can serve as an initial test. However, if the results do not align with the patient's clinical progress, it should be followed by a measurement of free testosterone. When a reliable method for measuring serum free

(or bioavailable) testosterone is accessible to the healthcare provider, and cost is not a major concern, this test is the preferred choice for initial testing.

The serum free testosterone concentration is roughly 50 percent more sensitive in detecting hyperandrogenemia compared to the total testosterone concentration. This heightened sensitivity is attributed to the characteristic low levels of SHBG (Sex Hormone Binding Globulin) in PCOS, which is the primary factor determining the proportion of serum testosterone that is either weakly bound to albumin or entirely free from protein binding, and thus bioactive(MOLL & ROSENFIELD JR, 1979; R. Rosenfield & Moll, 1983). As a result, when there is both an upper-normal total testosterone level and a lower-normal SHBG level, it leads to a significantly elevated free testosterone concentration. The production of SHBG by the liver is increased by estrogen and hyperthyroidism, while it is suppressed in situations involving hyperandrogenemia and/or hyperinsulinemia, which are commonly observed in cases of insulin resistance caused by obesity(Pugeat et al., 2010). While low SHBG levels in obese individuals have been linked to hyperinsulinemia(Nestler et al., 1991), there is evidence to suggest that the reduction in SHBG is also mediated by excessive consumption of glucose and fructose, as well as inflammatory cytokines, in individuals with obesity(Simó, Barbosa-Desongles, Lecube, Hernandez, & Selva, 2012).

The typical upper limit for serum total testosterone in adult women is approximately 40 to 60 ng/dL (1.4 to 2.1 nmol/L) when employing most validated assays(Goodman et al., 2015; Tosi et al., 2016). The

reference range for adults is generally considered appropriate for adolescents(R. L. Rosenfield, 2015; Witchel et al., 2015). The majority of patients with PCOS typically have serum testosterone concentrations ranging from 29 to 150 ng/dL (1 to 5.2 nmol/L). When total testosterone exceeds 150 ng/dL (5.1 nmol/L), it raises the suspicion of a virilizing ovarian or adrenal neoplasm. This cutoff point provides an approximate sensitivity of 90 percent and specificity of 80 percent for detecting androgen-producing tumors in adults(Sharma, Kapoor, Singh, Chang, & Erickson, 2018).

Ultrasonography

Ultrasonography is primarily employed in hyperandrogenemic adolescents to rule out potential causes of hyperandrogenism other than PCOS. It serves as a valuable tool for this purpose. Additionally, ultrasonography can have a secondary benefit in identifying individuals with markedly enlarged ovaries, which further supports the diagnosis of PCOS and enhances diagnostic specificity in such cases. In PCOS, ultrasound may reveal specific findings like a homogeneous and thickened endometrium. The ultrasonographic finding of polycystic ovarian morphology (PCOM) can be supportive of a diagnosis of PCOS, but it is not included in the 2015 diagnostic criteria for PCOS in adolescents. However, it's important to note that ultrasonography is neither recommended nor required for diagnosing PCOS in adolescents. This is because the prevalence of polycystic-appearing ovaries is relatively high among normal females in this age group, making it an unreliable criterion for the diagnosis of PCOS. Instead, clinical and

biochemical criteria are typically given greater emphasis when evaluating PCOS in adolescents(Yoost & Savage, 2019).

Diagnosis

A diagnosis of PCOS can be established when a patient consistently exhibits abnormal uterine bleeding patterns and evidence of hyperandrogenism after other potential causes of hyperandrogenemia have been excluded. The diagnosis of PCOS is often based on a combination of clinical symptoms, such as irregular menstrual cycles and signs of hyperandrogenism, along with the exclusion of other conditions that can cause similar symptoms. It's important for healthcare providers to thoroughly evaluate the patient and rule out other potential underlying causes before making a diagnosis of PCOS. Most clinical guidelines do recommend screening for conditions such as nonclassic congenital adrenal hyperplasia (NCCAH), Cushing's syndrome, prolactin excess, thyroid dysfunction, and acromegaly in individuals with hyperandrogenism. However, the specific tests and the criteria for screening can vary among guidelines. Some guidelines recommend universal screening for all patients with hyperandrogenism, while others suggest targeted screening based on the presence of symptoms suggestive of one of these disorders.

Treatment of polycystic ovary syndrome in adolescents

Indeed, the selection of therapy for PCOS should be tailored to the specific symptoms and goals of the individual adolescent, taking into consideration her preferences and overall health.

- In many cases, the first-line treatment for PCOS is estrogen-progestin combination oral contraceptives (COCs). These medications are often recommended because they can effectively address both menstrual irregularities and hyperandrogenism, which are common features of PCOS(Teede et al., 2018; Yoost & Savage, 2019)
- When hirsutism is not adequately controlled by cosmetic measures and estrogen-progestin combination oral contraceptives (COCs), healthcare providers may consider adding antiandrogen medications and/or direct hair reduction therapies to the treatment plan(Martin et al., 2018).
- Lifestyle modification is the initial approach recommended as the primary treatment for addressing overweight and obesity often linked to PCOS(Ibáñez et al., 2017; Styne et al., 2017)
- When weight loss alone cannot normalize abnormal glucose tolerance or lipid abnormalities associated with metabolic syndrome, when the primary objective is to restore ovulation, or when personal preferences do not align with the use of combination oral contraceptives (COCs), the use of metformin as a treatment option may be considered beneficial.

The estrogen component of combination oral contraceptives (COCs) helps reduce excess androgen levels, leading to a swift correction of menstrual irregularities and gradual improvement in hirsutism and acne. Noticeable effects of COCs on hirsutism typically become apparent after three to six months of continuous therapy. Use of a COC with antiandrogenic or minimal androgenic activity may be preferred.

As a general guideline, the use of combination oral contraceptives (COCs) is often recommended to be continued until the patient reaches gynecological maturity, which is typically defined as being five years postmenarcheal. Alternatively, COCs may be continued until a substantial amount of excess weight has been lost, depending on the individual patient's circumstances and treatment goals.

In cases where an adolescent patient is unable or unwilling to take combination oral contraceptives (COCs), the primary alternative therapeutic option for addressing menstrual irregularities is progestin

In adolescents with PCOS and obesity, weight loss has been shown to have positive effects on menstrual regularity, acanthosis nigricans, and hyperandrogenemia. The weight-reduction measures recommended, such as exercise and dietary changes, are generally similar to those advised for individuals with obesity who do not have PCOS. These lifestyle modifications aim to improve overall health and can be particularly beneficial for managing PCOS-related symptoms in adolescents.

Insulin-lowering agents have demonstrated the ability to enhance ovulation in around half of PCOS cases while modestly reducing androgen levels. However, it's important to note that they are generally less effective compared to combination oral contraceptives (COCs) in regulating menstrual cycles and managing hirsutism. Among these agents, metformin is the most commonly used in adolescents with PCOS. It serves a dual purpose by addressing coexisting insulin resistance and metabolic abnormalities, as well as functioning as an

adjunct to weight-control measures in the management of PCOS in adolescents

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CHAPTER IX

POLYCYSTIC OVARY SYNDROME AND ANDROGENIC HORMONES

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Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorderseffecting the women of reproductie age. It is characterized by a range of hormonal imbalances and clinical manifestations. Menstrual dysfunction, including oligo- or anovulation and signs of hyperandrogenism are the characteristics of PCOS (1).

One of the hallmark features of PCOS is the disruption in steroid hormone metabolism, leading to hormonal imbalances and various clinical manifestations.

Hyperandrogenism is one of the most important features of PCOS and contributes to hirsutism, acne, and alopecia. The androgenic hormones elevating in women with PCOS are free testosterone, total testosterone, DHEA sulfate (DHEAS), dehydroepiandrosterone (DHEA) and androstenedione.

Androgenic Hormone Metabolism and Control of Androgen Production

In women, the source of androgens are adrenal glands, ovaries and peripheral conversion of less potent to more potent androgens. In ovulatory women, ovaries and adrenal glands produce equal levels of testosterone and androstenedione. In PCOS, there is often an increase in androgen production. Elevated levels of luteinizing hormone (LH) and insulin are the main factors causing hyperandrogenism in PCOS.

The ovaries of women with PCOS have heightened sensitivity to luteinizing hormone (LH). Elevated levels of LH stimulate theca cells to produce excess androgens. The theca cells receive signals from insulin. Insulin resistance leads to higher androgen production. Insulin resistance is common in PCOS and it is a very important factor disrupting steroid hormone metabolism. Insulin resistance contributes to hyperinsulinemia and elevated levels of insulin stimulatates excessive production of androgens by ovarian theca cells. Additionally, insulin resistance can impact sex hormone-binding globulin (SHBG) production by liver, influencing the bioavailability of hormones. The ovaries become a significant source of androgen overproduction in PCOS.

The excessive androgen production stems from both ovarian and adrenal sources. Dysregulation in the enzyme activity within the steroidogenesis pathways, such as 17α-hydroxylase and 17,20-lyase, can lead to increased androgen synthesis.

Androstenedione synthesized by theca cells diffuses into nearby granulosa cells within the ovary. Inside the granulosa cells, androstenedione encounters the enzyme aromatase. Follicle-stimulating hormone (FSH) stimulates the granulosa cells to produce aromatase and aromatase converts the androgen precursors to estrone and estradiol (2). In women with PCOS, a higher level of Anti mullerian hormone (AMH) level is encountered (3). Increased concentrations of AMH may decrease stimulation of follicle growth by FSH and decrease aromatase enzyme activity. That results in inhibition of estradiol production. Elevated AMH contributes to the androgen

dominant milieu detected in the follicles of PCOS women.

Among the circulatin androgens, testosterone is the most potent one. The biological activity of testosterone is determined by its concentration, the level of sex hormone-binding globulin (SHBG) and its peripheral convertion to dihydrotestosterone (DHT) by the 5-alpha reductase enzyme. DHT binds to androgen receptors with a ten times greater affinity than testosterone. PCOS patients have a higher 5-alpha reductase activity (4).

Androgens and insulin decrease whereas estrogens increase the liver production of SHBG. As the women with PCOS are hyperandrogenic and most are obese and have insulin resistance, they have lower SHBG. That results in excess active free testosterone concentrations in circulation.

The potent intracellular androgen DHT is metabolised to 3-alpha-androstanediol-glucuronide (3aA-G). Urine concentrations of 3-aA-G are elevated in women with PCOS (5). The measurement of 3aA-G levels is not necessary for evaluation of hirsutism in PCOS.

Androstenedione is a testosterone precursor and it is also converted to estrone and estradiol in granulosa cells of ovary. Luteinizing hormone (LH) directly stimulates thecal secretion of androstenedione. As LH levels increase in PCOS, thecal androstenedione production increases. In PCOS cases, theca cells are also more sensitive to LH stimulation for androgen production (6). The secreted androstenedione is converted to testosterone by the peripheral tissue.

Dehydroepiandrosterone sulfate (DHEAS) is an androgenic hormone mostly secreted from adrenal glands. A small amount of DHEAS is produced by the peripheral convertion of Dehydroepiandrosterone (DHEA) to DHEAS by sulfokinase (sulfotransferase) activity in peripheral tissue. Both DHEA and DHEAS are markers of adrenal androgen production. Androstenedione and testosterone are the cause of hirsutism and virilization caused by adrenal hyperandrogenism.

Management of Hyperandrogenism in PCOS Patients

Hyperandrogenism treatment in PCOS patients is determined in 2018 Endocrine Society Clinical Guidelines (7).

First line treatment suggested for hyperandrogenism is combined estrogen- progestin oral contraceptives (COCs) if the patient's clinical features are appropriate and has no contraindications to take COCs. COCs have several mechanisms of action in treatment of hyperandrogenism. These are; inhibition of gonadotropin secretion (8-11), increasing the level of SHBG (11-13), reduction in serum total and free testosterone concentrations (8-10,14,15). To make any changes in dose, for adding a medication or for changing the medication, a clinician should wait at least for six months. Because a hair follicle grows in six months. After six months of period, if the clinical response is suboptimal to COCs treatment, spironolactone is added as an antiandrogen (7). The other antiandrogens used for the management of hyperandrogenism are; finasteride and flutamide. Flutamide is not suggested for treatment because of it hepatotoxic effects.

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CHAPTER X

NEW BIOCHEMICAL MARKERS IN THE DIAGNOSIS OF PCOS

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common causes of endocrinological and metabolic pathologies in reproductive age women. The prevalence of the complaint has been shown to be 5-15 in different studies. Clinical symptoms vary depending on the factors delved , similar as inheritable factors and environmental factors that affect the complaint. Heterogeneous patient structure makes diagnosis difficult. Therefore, for the opinion of the complaint, individual criteria created by the combination of clinical symptoms, laboratory results and imaging results according to different concurrences have been developed. Over the times, numerous scientific studies have been carried out using these individual criteria. In line with these studies, some diagnostic criteria needed to be updated. For this reason, in some studies, the etiology and pathophysiology of pcos were investigated, and the markers that could provide a more accurate and faster diagnosis of the disease were examined.

MARKERS

In PCOS patients many different markers, varying on a patient basis, have been investigated due to their clinical structures and multisystem effects. The detection successes of different serum markers related to the diagnosis and level of the disease were evaluated. In these studies, many biochemical markers such as basal hormone levels (follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin), androgen levels (free/total testosterone, dihydrotestosterone), blood glucose level and insulin level, serum lipid profile (triglyceride,

HDL, total cholesterol), albumin levels, C-reactive protein (CRP) levels, oxidative stress markers (glutathione, malondialdehyde, total antioxidant capacity), HOMA-IR were examined. As a result of these examinations, significant data were obtained in patient groups with various phenotypes. With new studies, markers that can give meaningful results in large patient groups are being investigated.

1)5a-antrostanedion: It plays a part in the conformation of dihydrotestosterone in hyperandrogenism by taking a part in androgen biosynthesis. It was set up to be significantly advanced in PCOS cases compared to the control group without PCOS.(Stanczyk FZ et al.,2023)

2)Vitamin D: Vitamin D plays a part in follicle development and insulin resistance mechanisms. Correlation with ovarian reserve has been demonstrated. Metabolic changes were set up to be associated with low serum vitamin d situations in cases with PCOS. (Mohan A et al.,2023)

3)Asprosin: It is a peptide hormone secreted by white adipose tissue. It has been set up to be associated with rotundity and insulin resistance by playing a part in hepatic glucose secretion.

Serum asprosin position was set up to be significantly advanced in women with PCOS than in women without PCOS. It has been shown that asprosin can be a new indicator in PCOS, especially in terms of evaluating insulin resistance. (Pérez-López FR et al.,2023)

4)Kispeptin: It's a peptide that plays a part in the regulation of the hypothalamo- pituitary system and the release of fsh- lh. There are studies showing that serum levels are higher in PCOS patients when their serum levels are evaluated with elisa. Especially obese PCOS patients were found to be more significant. It has also been shown to relate with blood situations of AMH.

5)Triglyceride-glucose index: Insulin resistance has an active part in the pathophysiology of PCOS. Triglyceride-glucose index gave significant results in studies on metabolic syndrome and insulin resistance. It can be thought as a good indicator for the detection of insulin resistance in PCOS patients. (Zhang L et al.,2023)

6) Uric acid: Serum uric acid level affects many body composition indicators such as body weight, body-mass index (BMI), waist-hip rate, body muscle mass, and body fat percentage. group in the PCOS case and control groups, which were estimated independently from fat andnon-obese. It was shown that the uric acid level was significantly advanced in the PCOS group in the PCOS patient and control groups, which were evaluated separately from obese and non-obese. It can be helpful in identifying and individualizing the treatment of PCOS patients at risk for metabolic abnormalities.

7)Adiponectins: They are synthesized from adipose tissue. It is a metabolic syndrome marker hormone that plays a part in the regulation of metabolic hemeostasis and insulin sensitivity.

Studies have shown that the rate of adipocyte-derived hormone leptin can be used to distinguish between PCOS and non-PCOS and to detect metabolic risk factors in patients with PCOS.

CONCLUSIONS

PCOS cannot be diagnosed with a single marker, unlike many diseases, due to its clinical features that may vary on a case- by- case base. Depending on the clinical symptoms accompanying the disease, some markers may be superior to others in diagnosing the diagnosis. In our article, in which we evaluated the results obtained from the current researches in the last 1 year, different results could be obtained with different markers. However, there is no marker that can be defined as the gold standard in diagnosis yet. Therefore, new studies are demanded to identify labels with high perceptivity and particularity that can be used in the clinical opinion of pcos.

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CHAPTER XI

POLYCYSTIC OVARY SYNDROME AND OBESITY

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POLYCYSTIC OVARY SYNDROME AND OBESITY

Polycystic ovary syndrome (PCOS) was first clinically described in 1935 (Stein & Leventhal, 1935). PCOS is the most common endocrinopathy in fertile age women and occurs in 6-10% of fertile age women (Azziz et al., 2004) (Barber et al., 2006). The prevalence of PCOS (according to Rotterdam diagnostic criteria) has been found to be up to 10% (Bozdag et al., 2016). PCOS typically manifests itself during puberty, especially with weight gain and obesity (Barber et al., 2006). Weight gain and obesity are common features of PCOS. Obesity is abnormal or excessive fat accumulation that negatively affects health. Although body mass index (BMI) has limits depending on ethnicity. BMI ≥25 kg/m2 are considered overweight and BMI ≥30 kg/m2 are considered obese (Nishida et al., 2010) (WHO, 2008). 38-88% of women with PCOS have been shown to be obese or overweight (Barber et al., 2006). Obesity is probably not a cause of PCOS and most women with PCOS are known to be of normal weight. Obesity exacerbates many aspects of the PCOS phenotype, particularly metabolically, glucose intolerance and cardiovascular risk such as dyslipidemia (Boomsma et al., 2006). Women with PCOS are frequently found to have visceral adiposity (Durmus et al., 2017). Increased weight gain (as well as dyslipidemia and hyperandrogenemia), especially in early adulthood, is associated with the development of PCOS (Ollila et al., 2016). Menstruation, ovulation, reproduction (including hyperandrogenic and dysmetabolic features) often improve in response to moderate (5-10%) weight loss in obese women with PCOS (Motta, 2012).

It is known that obese women with PCOS have a more severe phenotype than less obese women. Obese woman have more severe menstrual irregularities, infertility, miscarriage, pregnancy-induced hypertension, gestational diabetes, prematurity, biochemical-clinical hyperandrogenism, metabolic syndrome, glucose intolerance and/or T2DM than less obese woman (Glueck et al., 2013) (Zeng et al., 2016).

Risk factors associated with obesity in PCOS

Many factors have been found to be associated with and/or promote the development and severity of PCOS. These include; born small for gestational age (SGA) (Melo et al., 2010) (Ibáñez et al., 1988) (Puttabyatappa et al., 2016) born large for gestational age (birth weight ≥4,500 g), being born to a diabetic mother (inversely related to birth weight) (Mumm et al., 2013), Maternal PCOS (Melo et al., 2010) (Puttabyatappa et al., 2016)exposure to intrauterine hyperandrogenism (Puttabyatappa et al., 2016), early pubarche (Ibáñez et al., 1988) early menarche (≤ 10 years) and late menarche (≥ 16) (Glueck et al., 2013), valproic acid use (Hu et al., 2011) is found.

Another factor contributing to weight gain in women with PCOS is ethnicity. It is known that the prevalence of impaired glucose tolerance and T2DM increases in women with PCOS. These increases have been shown to vary by ethnicity (BMI compatible subgroups in Asians and Europeans) and obesity has also been shown to be higher. (Kakoly et al., 2018).

The rs9939609 A/T polymorphism, which is one of the polymorphisms in the fat mass obesity and obesity-related (FTO) gene, has been shown to be significantly associated with PCOS risk in Asians and Caucasians (Liu et al., 2017).

The increased association of anxiety (commonly seen), depression, and binge eating behaviors with PCOS (Gambineri et al., 2002) are external factors that contribute to obesity in PCOS (Horejsi et al., 2004).

Genetic links between PCOS and obesity

PCOS is associated with obesity, which is heavily influenced by genetic variants. PCOS is a disease with a hereditary component of approximately 70%. (Barber & Franks, 2012). In a large-scale study, the similarity of symptoms for PCOS in monozygotic twin sisters (70%) was found to be approximately twice that of dizygotic twins and other sisters. (Vink et al., 2006). 35% of mothers and 40% of sisters of women with PCOS have features of the PCOS syndrome (Kahsar-Miller et al., 2001). In addition, as in women with PCOS, the incidence of dyslipidemia and insulin resistance was found to be high in male relatives of women with PCOS (Sam et al., 2008).

Studies have shown that there is a relationship between obesity and single nucleotide pleomorphisms (SNPs) related to the FTO gene. In particular, SNPs occurring in the first nitron of the FTO gene (rs9939609) and mutations in the FTO gene have been shown to be associated with obesity and increased fat mass (Zhao et al., 2014) (Liu et al., 2017). In some studies, no relationship was found between FTO

gene polymorphisms and obesity, and it was stated that ethnic origin and FTO gene polymorphism may play an important role in the development of obesity (Pereira et al., 2016) (Liu et al., 2017). It has also been reported that FTO and Melanocortin-4 receptor (MC4R) gene variations are associated with the development of obesity in women with PCOS (Ewens et al., 2011).

Visceral Fat

Patients with PCOS, whether obese or not, have been shown to have more visceral adiposity than controls (Jena et al., 2018). Testosterone inhibits lipolysis and promotes lipogenesis. And so testosterone increases visceral fat deposition and insulin resistance (Rosenfield & Ehrmann, 2016). Women with PCOS have been shown to be more likely to be obese than female controls without PCOS. Additionally, women with PCOS are much more likely to have visceral adiposity and high visceral adiposity indices, associated with some metabolic and inflammatory parameters. These are also closely related to insulin resistance (Durmus et al., 2017).

Obesity-related metabolic consequences in PCOS

The prevalence of insulin resistance in women with PCOS has been shown to be 25-70% (Boomsma et al., 2006). Insulin resistance (IR) is higher in patients with PCOS than in the general population. IR favors the development of PCOS. Insulin sensitivity in PCOS is 27% lower than in the control group. It has also been shown that high BMI exacerbates the decrease in insulin resistance by 15% (Cassar et al.,

2016). Obese women with PCOS have been shown to have a 7- to 10-fold increase in the rate of conversion from normal glucose tolerance to impaired glucose tolerance, or T2DM, compared with normal-weight individuals (Norman et al., 2001). Overweight and obesity in PCOS with concomitant androgen excess (Glueck et al., 2005) increases adverse metabolic outcomes and doubles the likelihood of T2DM (Norman et al., 2001).

Both obese and non-obese women with PCOS have been shown to have increased insulin resistance, increased T2DM, and increased risk of cardiovascular disease (associated with metabolic syndrome). Cardiovascular risk in PCOS has been shown to be related to BMI (Glintborg et al., 2018). By the age of 40, it has been estimated that up to 40% of all women with PCOS will develop type II diabetes or impaired glucose tolerance (Boomsma et al., 2006).

Obesity is known to potentiate and worsen all metabolic and reproductive outcomes in women with PCOS. Obesity is known to be the most common cause of insulin resistance. Compensatory hyperinsulinemia increases due to the insulin resistance that develops in obesity. Hyperinsulinemia increases adipogenesis and reduces lipolysis in tissues. Obesity upregulates ovarian androgen production by sensitizing theca cells to LH stimulation, resulting in enhanced functional ovarian hyperandrogenism. In addition, obesity increases insulin resistance and adipogenesis by increasing inflammatory adipokines. Increased insulin resistance provides a vicious feedback loop that increases obesity (Figure 1) (Glueck & Goldenberg, 2019).

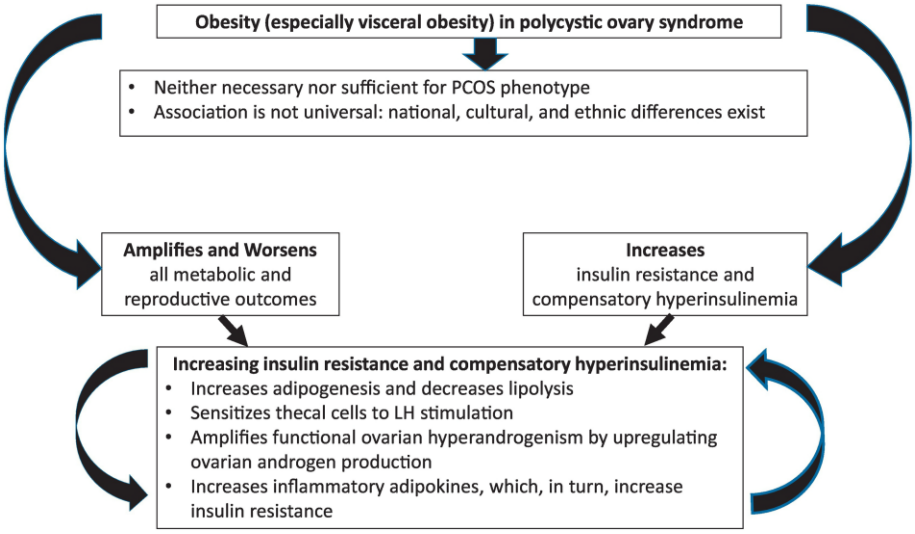

Figure 1. The effect of hyperinsulinemia in obesity (Glueck & Goldenberg, 2019)

In overweight or obese women with PCOS (compared to non-overweight women with PCOS), decreased sex hormone binding globulin (SHBG), increased testosterone (T), increased free androgen index (FAI), more hirsutism, higher fasting glucose and increased insulin resistance (IR) has been found. Furthermore, obesity has been shown to worsen all measured metabolic and reproduct ive outcomes except hirsutism compared to normal weight women with PCOS. Central obesity has been shown to be associated with higher serum insulin levels (Lim et al., 2013)

Reproductive effects of obesity in PCOS

It has been shown that women with PCOS have higher risks of pregnancy complications (gestational diabetes mellitus, pregnancy-induced hypertension and pre-eclampsia) and neonatal complications (preterm delivery, neonatal intensive care unit admission and perinatal mortality). Increased risk of developing gestational diabetes in women

with PCOS occurs independently of obesity. No significant changes in neonatal birth weight (small for gestational age or macrosomic) or increased incidence of congenital malformations were observed in infants born to women with PCOS. There was no significant change in neonatal birth weight (small for gestational age or macrosomic) and no increase in the incidence of congenital malformations in infants born to women with PCOS. There was no increase in the rate of caesarean delivery and instrumental delivery in women with PCOS (Boomsma et al., 2006).

PCOS is known to be one of the leading causes of infertility. Most women with PCOS are overweight or obese. Obesity increases the risk of subfecundity and infertility through disruption of the hypothalamic-pituitary-ovarian axis, poor oocyte quality and altered endometrial receptivity. Obesity attenuates the response to infertility treatment in patients with PCOS. Increasing BMI in PCOS increases clomiphene resistance and decreases responsiveness to gonadotropins or the chance of conception by in vitro fertilization. A decrease in 5 BMI units has been shown to result in little or no increase in live birth rates. Further changes in weight may lead to positive changes in circulating biochemical markers such as the free androgen index or insulin-like growth factor-1, which may increase treatment success (Legro, 2012).

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CHAPTER XII

POLYCYSTIC OVARY SYNDROME AND OXIDATIVE STRESS

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Introduction

According to numerous studies, oxidative stress markers rise in women with polycystic ovarian syndrome (PCOS) than healthy women and have significant roles in the pathophysiology of this condition. Obesity, insulin resistance, excess androgen, abdominal adiposity, and other aspects of PCOS may have roles for the development of systemic and local oxidative stress, which may in turn exacerbate the metabolic abnormalities.

PCOS is a widespread metabolic and reproductive disorder in women. Since PCOS is a metabolically unstable syndrome, an elevated cardiovascular risk might be expected (Macut et al., 2013). PCOS is linked to metabolic and long-term health risks like insulin resistance, type 2 diabetes, dyslipidemia, aelevated risk of impaired glucose tolerance, metabolic syndrome (MS), as well as reproductive and obstetric issues like hyperandrogenism (HA), infertility, menstrual dysfunction, and pregnancy complications. It is also linked to increased oxidative stress, systemic low-grade chronic inflammation, and a possible elevated risk of cardiovascular disease (Zhang et al., 2012).

2. Oxidative stress

The imbalance of oxidants and antioxidants as well as the excessive production of ROS (reactive oxygen species) are referred to as oxidative stress. Many studies showed that oxidative circulating indicators are much higher in PCOS women compared to controls, and they are believed to be a potential initiator of PCOS pathogenesis (Murri et al., 2013). The importance of oxidative stress in the aetiology

of several disorders, including PCOS, is now accepted widely. Although highly complicated antioxidant enzyme and non-enzymatic systems regulate intracellular ROS formation and propagation, knowing the mechanisms of oxidative stress is essential in establishing prevention and treatment plans for PCOS (Mohammadi, 2019).

PCOS-related oxidative stress may be brought on by a wide range of metabolic and endocrine disorders, including hyperinsulinemia, obesity, and dyslipidemia. Diabetes dyslipidemia was not significantly affected by therapeutic interventions in PCOS patients based on lifestyle changes or the use of insulin sensitizers. Statins are seen to be a promising class of drugs that have antioxidant activity in addition to being safe and effective for lowering triglycerides, LDL cholesterol, and total cholesterol. Omega-3 fatty acid, -lipoic acid, and N-acetylcysteine supplementation is thought to have an antioxidant and anti-inflammatory impact, as well as enhance insulin sensitivity and dyslipidemia in PCOS women (Macut et al., 2013).

Age-related cardiovascular disease (CVD) risk is amplified in PCOS-affected women due to lifelong metabolic abnormalities. Insulin resistance, which affects the majority of women with PCOS, has historically and physically been associated with metabolic dysfunction. It seems to arise independently and additionally to insulin resistance in obese people without PCOS. Understanding PCOS is interesting from a lipid metabolism point of view because the PCOS phenotype is an amazing biological experiment in nature. In women with PCOS, there is an excess of androgen, IR, different levels of oestrogen exposure, and a variety of environmental factors, all of which might affect how lipids

are metabolised. A uncommon hereditary lipid condition like heterozygous familial dyslipidemia can exist in women with PCOS, just like it can in any woman. Women with PCOS may also be affected by lipid metabolism due to ageing, obesity, lifestyle factors (such as physical inactivity, diets high in sugar and saturated fat and low in fibre, smoking, and illegal drugs use), and medication use (Wild, 2012).

Both non-obese and obese PCOS women experience oxidative stress (Liu & Zhang, 2012; Desai et al., 2014). Both enzymatic and non-enzymatic endogenous antioxidants are disrupted in PCOS patients; this can also be brought on by hyperglycemia, a condition that frequently co-occurs with PCOS and triggers pathways resulting with the production of ROS. As a result, the equilibrium is upset and oxidative stress is elevated (Zhao et al., 2015). PCOS is typically accompanied with insulin resistance, which causes the pancreatic beta cells to release more insulin. Due to this, ROS levels rise, which causes the activity of the antioxidants to decline (Moran et al., 2010). It also was shown that insulin resistance promotes leukocyte adhesion to the epithelium as well as oxidative stress in cells, which can be a factor in a few clinical issues seen in PCOS patients (Victor et al., 2016).

3. Oxidative stress biomarkers in PCOS

3.1. Malondialdehyde (MDA)

Malondialdehyde (MDA) is a physiological ketoaldehyde produced as a result of arachidonate metabolism by the peroxidative breakdown of unsaturated fats. It is produced during the synthesis of prostaglandins and by the peroxidation of membrane polyunsaturated fatty acids.

According to Roede and Fritz (2015), MDA has long been used as the main biomarker of lipid peroxidation. Increased lipid peroxidation, which results in the production of MDA, coupled dienes, coupled diene hydroperoxides, and oxycholesterols, are changes in the lipid profile that come along with PCOS (Szczuko et al., 2019).

According to a study by Fan et al. (2012), along with other associated risk factors, decreased apoE-containing and total HDL-PAF-AH activities, increased MDA concentration, and PCOS pathogenesis may all be affected and may be connected to associated issues, such as an elevated risk for future cardiovascular disorders and/or type 2 diabetes mellitus in PCOS patients, which are the cause of oxidative stress and inflammation. According to a meta-analysis, the mean MDA concentrations in the blood tests of PCOS patients were 47% higher than those of controls according to their age and BMI (Murri et al., 2013)

Blood MDA levels were studied between healthy controls and PCOS patients by Kuscu et al. in 2009. They demonstrated that, despite being unrelated to fat, the MDA level was noticeably greater in the PCOS group. BMI and age were not taken into account, but Zhang et al. (2008) revealed that serum MDA level values were considerably greater in PCOS group than in the control group. Palacio et al. (2006) contrasted PCOS patients with controls who were age- and BMI-matched. They showed that erythrocyte MDA levels were greater in PCOS patients than controls.

3.2. Homocysteine

As a byproduct of methionine metabolism, homocysteine is a sulfur-containing amino acid. It is a step in the trans-sulfuration process, which turns methionine into cysteine biochemically. B-vitamins, including folate, vitamin B6, vitamin B12, and riboflavin, are needed for the breakdown of homocysteine. Homocysteine levels in the blood rise (hyperhomocysteinemia) when homocysteine metabolism is disrupted by B-vitamin shortages, genetic abnormalities, or other pathophysiological circumstances. Vascular disease, neurological diseases, and other clinical diseases are all at risk due to hyperhomocysteinemia. Thus, homocysteine may serve as a risk factor for vascular disease but not as its primary cause (Miller, 2023).

Salehpour et al. (2011) evaluated the plasma homocysteine levels of PCOS patients and healthy controls. Homocysteine levels were 16.25 11.94 mol/L on average in PCOS patients compared to 11.58 3.82 mol/L on average in controls (p=0.002). Comparing patients with PCOS to BMI-matched control women, patients with PCOS exhibited a considerably increased incidence of hyperhomocysteinemia. These findings imply that homocysteine levels are elevated in PCOS patients. In-depth research is required to define this connection.

According to Mohammedi et al. (2010), homocysteine levels greater than 11 mol/L are seen in 30% of patients, which triples the death rate. In order to determine whether hyperhomocysteinaemia occurs in PCOS and whether it is associated with insulin resistance in the affected patients, Hemati et al. (2011) conducted research. They discovered that insulin resistance and hyperhomocysteinemia are predisposed in PCOS

patients. Patients who are insulin resistant have greater homocysteine levels.

3.3. Advanced glycosylated end products (AGEs)

The glycation reaction, which is defined as the irreversible attachment of a carbohydrate to a protein without the assistance of an enzyme, produces molecules known as AGEs (Advanced glycation end-products) (Boemi et al., 2016). A combination of amino groups found in lipids, proteins, and nucleic acids, also reducing carbohydrates like glucose, combine irreversibly through nonenzymatic interactions to form AGEs. It is thought that oxidative stress is the end result of the interaction between AGE and the AGE receptor (RAGE). Since the oxidation of circulating glucose is the main source of endogenous AGE, hyperglycemia makes AGE formation worse (Bloemer et al., 2014).

When AGEs attach to related cell membrane receptors (RAGE), they produce a condition of inflammation and intracellular oxidative stress. Elevated serum/ovarian AGE levels and eexpression of the pro-inflammatory RAGE in ovarian tissue are indicators of a systemic chronic inflammatory disease in women with PCOS. According to data from Pertynska-Marczewska et al. (2015), soluble receptor for AGEs (sRAGE) is present in the follicular fluid and may play a protective role against the negative effects of AGEs on ovarian function. Accumulating data suggests that AGEs may alter steroid biosynthesis in polycystic ovaries by influencing enzyme performance, inducing inflammatory alterations, and insulin resistance. AGEs level as an oxidative stress marker of PCOS has been described in various investigations (Garg & Merhi, 2016). Elevated androgen production and aberrant

folliculogenesis may occur from abnormal steroidogenesis in PCOS (Diamanti-Kandarakis, 2008).

Tantalaki et al. (2014) investigated on how AGE dietary intake affected the hormonal status of PCOS-afflicted women. They provided PCOS patients an isocaloric diet with either a high or low AGE content for two months, and they observed that the H-AGE diet resulted in greater serum AGE coupled with enhanced levels of testosterone, the free androgen index, and androstendione.

3.4. Xanthine oxidase (XO)

"Xanthines" are a class of alkaloids that are frequently used for their actions as bronchodilators and mild stimulants, particularly in the treatment of asthma symptoms. Therefore, it is crucial to detect these molecules, and electrochemical biosensors have been used in this process. Reactive oxygen species are produced by a group of enzymes called xanthine oxidases (XOxs). These enzymes can also catalyse the oxidation of xanthine to uric acid after oxidising hypoxanthine. According to Fritea et al. (2018), these enzymes are crucial for the breakdown of purines in humans.

"Xanthine oxidase" (XO) is a homodimer cytosolic enzyme with a molecular mass of 300 kDa that contains molybdenum (Mo). It is essential in the body's process of converting xanthine and hypoxanthine to uric acid (UA). Due to UA's limited solubility, excessive UA levels in the blood may result in the development of urate crystals, which are then deposited in tissues including cartilage and joints. Inflammation from excess urate crystals finally gave rise to gout. As a result, XO is a

key consideration when evaluating substances to lower UA, and research into XO inhibitors has gained increased attention (Li et al., 2022). In PCOS women, the mean CRP has a negative correlation with SOD activity and a positive correlation with XO activity (Isık et al., 2016).

3.5. Nitric oxide (NO)

Insulin resistance and follicular maturation arrest are listed as the most significant ovarian symptoms in anovulatory women with PCOS (Manneras et al., 2007). Increased levels of endothelin-1, one of the primary indicators of vascular disease, and decreased production/release of endothelium-derived nitric oxide (NO), have been linked to the latter phenomena (Nacul et al., 2007). Currently, PCOS is classified as an inflammatory syndrome. The NO molecule is widely known for causing localised inflammation, and it is also listed among the causes of PCO syndrome and the ovulatory processes (Liu et al., 2006).

Hassani et al. (2012) employed Wistar rats administered with L-Arginine, a precursor of NO, to investigate the function of NO in PCOS. The results revealed that, in contrast to control rats, the ovaries of the L-Arginine-treated rats had polycystic characteristics, leading the researchers to speculate that NO may be an important factor in the pathophysiology of PCOS. By measuring NO in PCOS patients and healthy controls, Karabulut et al. (2012) studied the relationship between PCOS and oxidative stress state. Results revealed that PCOS patients had statistically greater NO levels than control women. In PCOS patients and controls with comparable age and BMI, Willis et al.

(2012) compared measurements of oxidative stress and NO metabolites. Results showed that participants with PCOS had lower nitrate levels but equivalent amounts of nitrite (nitrite/nitrate concentration is a measure of NO generated from the endothelium). NO levels in PCOS patients were equivalent to controls who were comparable for age and BMI, according to Nacul et al. (2007). They evaluated NO and fibrinogen levels as two indicators of vascular disease linked to insulin resistance in PCOS women, and they found a substantial inverse relationship between NO and fasting insulin levels as well as evaluation of the homeostatic model. They claimed that NO and the existence of insulin resistance in PCOS patients were connected.

4. Anti-oxidative stress markers in PCOS

4.1. Superoxide dismutase (SOD)

The SODs (superoxide dismutases) are a class of metalloenzymes that produce triplet oxygen and hydrogen peroxide from two superoxide anions. By converting the superoxide anion to oxygen and hydrogen peroxide, the antioxidant enzyme SOD scavenges the free radical and stops the synthesis of peroxynitrite and further damage. This scavenging capacity of SOD has attracted plenty of interest for therapeutic usage. Applications for SOD include anti-inflammatory, anti-tumor, radiation protection, and anti-senility applications (Wang & Zhang, 2015).

Compared to controls, a small number of studies have found that patients with PCOS have higher levels of SOD (Jeelani et al., 2019). In

contrast to this finding, some research (Masjedi et al., 2019; Enechukwu et al., 2019) revealed a lower level of SOD in PCOS participants. According to Zhang et al. (2008), PCOS patients had significantly lower serum SOD levels than the control group. In a young, non-obese cohort of PCOS patients, Kuscu & Var (2009) analysed blood SOD levels to investigate the impact of oxidative stress in endothelial dysfunction. They demonstrated that the PCOS group's SOD levels were significantly higher than those of the control group. In the meta-analysis of Murri et al., (2013) showed that the mean SOD activity was 34% higher in PCOS patients than in controls.

Seleem et al. (2014) examined at the SOD activity in the follicular fluid (FF) and serum of PCOS women receiving intracytoplasmic sperm injection. They found a statistically significant decrease in SOD activity in PCOS compared to the control group, both in the mean serum and FF, and they hypothesised that serum SOD activity could be a clinical indicator for identifying systemic oxidative stress in PCOS. Single-nucleotide polymorphisms (SNP) of SOD1 are thought to be connected to intra-individual variances, which may also be related to SOD activity variability and the detrimental effects of oxidative stress. One of these might be the SOD1 gene's rs2070424 (A251G) (Silig et al., 2017). This polymorphism could be associated with increased body fat, impaired glucose regulation, type 2 diabetes and inflammation, which are common disorders observed in the course of PCOS (Bizon et al., 2022.

However, because to SOD's highly rapid plasma clearance time, instability, and immunogenicity in vivo, its clinical use as a therapeutic agent has been constrained. To address these issues, a number of

methods have been suggested, such as the use of SOD conjugates with alginate-chitosan or hydrophilic polymers, such as PEG, as suitable vehicles for delivery (Wang & Zhang, 2015).

4.2. Glutathione peroxidase (GPx)

A selenium-containing enzyme called glutathione peroxidase (GPx) reduces organic hydroperoxides (ROOH) and hydrogen peroxide while utilising glutathione (GSH) as a hydrogen donor. According to Tabet and Touyz (2007), GPx efficiently converts H2O2 and lipid peroxides into water and lipid alcohols, respectively, and then oxidises glutathione to glutathione disulfide. The detoxification of lipid peroxides is carried out by the glutathione peroxidase family (Gpx1, Gpx2, Gpx3, Gpx4), which includes glutathione peroxidase 4 (Gpx4). While all glutathione peroxidases are capable of destroying hydrogen peroxide, alkyl peroxide, and fatty acid hydroperoxides, only Gpx4 is able to destroy the hydroperoxides that are present in lipoproteins and complex lipids like those made of cholesterol, cholesteryl esters, and phospholipids (Lustgarten et al., 2011).

Baskol et al. (2012) measured GPx activity in PCOS patients and age- and sex-matched healthy controls to study the relationship between oxidative stress and the antioxidant system in the development of PCOS. According to the findings, there was no discernible difference between the GPx activities of PCOS patients and control women. According to one meta-analysis (Murri et al., 2013), there was no statistically significant difference between the mean GPx activity in women with PCOS and controls. Savic-Radojevic et al. (2015)

demonstrated that PCOS women's GPx activity dramatically declines when compared to controls.

4.3. Total antioxidant capacity (TAC)

According to a meta-analysis, there was no discernible difference in TAC between women with PCOS and controls (Murri et al., 2013). Fenkci et al. (2003) compared the TAC level in PCOS patients to controls who were similar in age, BMI, and smoking status. They showed that patients with PCOS had significantly decreased TAC levels. However, Verit & Erel (2008) found that TAC levels in PCOS patients were considerably greater than in controls with same age and BMI. They suggested that TAC was increased to restore the oxidative stress elevation, even if the full mechanism of this elevation is unknown.

5. Conclusion

Women with PCOS exhibit aberrant circulating oxidative stress indicators, regardless of excess weight. NAD(P)H oxidases, xanthine oxidases, and cyclooxygenase, among others, may generate superoxide anion. The SOD converts superoxide anion to hydrogen peroxide. Catalase or the enzyme glutathione peroxidase, which needs GSH as an electron donor, can scavenge hydrogen peroxide. Glutathione reductase converts the oxidised glutathione back to GSH. Hydrogen peroxide can be broken down by some transition metals into the reactive hydroxyl radical. The polyunsaturated fatty acid, DNA, or proteins can all lose an electron at the handle of the hydroxyl radical. The reduced form of Vitamin E, which can be restored by Vitamin C, or GPx employing

GSH as the electron donor can both reduce lipid hydroperoxides. Peroxynitrite anion, a strong oxidising agent that can lead to protein, DNA, and lipid oxidation, is generated when nitric oxide synthase, which generates nitric oxide, reacts with the superoxide anion.

According to numerous studies, oxidative stress markers rise in women with polycystic ovarian syndrome (PCOS) compared to healthy women and play a key role in the pathophysiology of the condition. Oxidative stress may be associated with PCOS. The PCOS prognosis may be improved by antioxidants.

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CHAPTER XIII

THE APPROACH TO INFERTILITY AND OVULATION INDUCTION IN PATIENTS DIAGNOSED WITH POLYCYSTIC OVARIES

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POLYCYSTIC OVARY SYNDROME AND INFERTILITY

In order for a woman of reproductive age to have regular ovulation, the hypothalamo-pituitary-ovarian axis must be functioning properly. A problem that occurs in this axis causes anovulation. Polycystic Ovary Syndrome (PCOS), which is the most common endocrine problem encountered in women of reproductive age, is also the most common cause of anovulatory infertility, hirsutism and hyperandrogenism in women of this period(1).

When looking at the frequency ranking of the signs and symptoms of polycystic ovary syndrome;

1. Hirsutism (60-90%)
2. Oligomenorrhea (50-90%)
3. Infertility (55-75%)
4. Polycystic ovarian morphology (50-75%)
5. Obesity (40-60%)
6. Amenorrhea (25-50%)
7. Dysfunctional uterine bleeding (30%)
8. Acne (25%)

A. PCOS DIAGNOSTIC CRITERIA

There have been many discussions about the diagnosis of the disease in the past, and different diagnostic criteria have been focused on different sessions. For the first time in 1990, the National Institute of Health

(NIH) addressed the issue of hyperandrogenism and ovarian dysfunction and emphasized that these two criteria should be both(2).

In 2003, at a meeting known as the Rotterdam criteria and sponsored by the European Society of Reproductive and Endocrinology (ESHRE) and the American Society of Reproductive Medicine (ASRM), they emphasized that hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology can be diagnosed with a disease with at least two of them(3).

In 2006, Androgen Excess – PCOS (AE-PCOS) stated that androgen elevation is the basis of this disease, so the diagnostic criteria definitely include clinical or laboratory findings of hyperandrogenism; ovarian morphology and ovulatory dysfunction ovulatory dysfunction will support the diagnosis.

After all these discussions, in 2012, NIH emphasized that the Rotterdam criteria should be applied exactly, but the disease should be studied under 4 phenotypes with the idea that it will facilitate future studies and facilitate treatment. Currently, the general opinion in clinical practice is that the Rotterdam criteria are used.

B. EPIDEMIOLOGY

The general prevalence of the disease is between 10-15% and we often come across complaints of alop Decia, hirsutism, amenorrhea and infertility. Considering that there are cardiac diseases, metabolic syndrome and oncological events in the long-term consequences of the disease, the importance of making a diagnosis at an early term is understood(4).

The disease differs according to geographical regions and ethnic groups, and the prevalence also varies, especially according to different diagnostic criteria. a meta-analysis published in 2016 found a worldwide PCOS prevalence of 6% according to the NIH criteria, 10% according to the AE-PCOS criteria and 10% according to the Rotterdam criteria(1).

Phenotyping conducted at the NIH meeting in 2012 showed that phenotypes A and B, in particular, are more prone to metabolic syndrome, insulin resistance, atherogenic events than other phenotypes due to their hyperandrogenism and ovulatory dysfunction(5). Again, in another study, it was noted that there are low clinical pregnancy rates in phenotype A and B compared to other types in assisted reproductive techniques used in PCOS cases who want to have a child(6).

C. PATHOPHYSIOLOGY

Although the etiology of polycystic ovary syndrome is not known for sure, it is believed that the disease has been known for a long time and that it is a disease caused by the interaction of genetic and environmental factors with the studies conducted. It is a multi-systemic disease that affects a large number of endocrine organs and also affects the metabolic system.

The basis of PCOS development is cronic anovulation. There is no progesterone synthesis due to the absence of ovulation. Therefore, there is a decrease in central opiate tone and gonadotropin-releasing hormone (GnRH) gets rid of this pressure. With an increase in GnRH pulsatility, especially the release of luteinizing hormone (LH) increases. An

increase in GnRH pulsatility definitely does not lead to an increase in follicle stimulating hormone (FSH) hormone secretion. This is due to the negative feed back effect of increased peripheral estrogens. For this reason, an increase in the LH/FSH ratio is expected in PCOS cases. However, this is not a diagnostic criterion.

With increased LH, the androgen production of teka cells increased. Sex hormone binding globulin (SHBG), which allows sex steroids to be transported in the blood, decreases in a highly androgenic environment, and therefore the active free forms of androgens increase. This leads to follicular atresia, anovulation and hirsutism(7).

With the increase of androstenedione, known as peripheral androgen, in circulation, peripheral aromatization increases and estrone (E1) increases in the blood. As a result, the estrone/estradiol ratio also increases, and oncological events such as endometrial hyperplasia and endometrial cancer occur in the long term due to unmet estrogen.

In studies conducted in cases of PCOS, a genetic disease, it has been observed that there is an autophosphorylation defect in insulin and CYP17 enzyme receptors (serine autophosphorylation instead of tyrosine). As a result, an increase in the activity of the p450c17 enzyme, which is involved in steroid synthesis, and insulin resistance occurred. Adrenal androgen production increased due to an increase in the activity of this p450c17 enzyme. In addition, insulin resistance due to the failure of the insulin receptor, increased insulin production with increased resistance leads to hyperinsulinemia and this leads to obesity.

The increase of insulin and insulin-like proteins (IGF-1) reduces the synthesis of SHBG, stimulates the production of androgen from the ovary and prevents the atresia of oocytes in the androgenic environment, prevents the selection of the dominant follicle and causes anovulation(8).

In one of the studies conducted in patients diagnosed with PCOS, hyperprolactinemia was detected in one out of every 4 patients diagnosed. In these patients, luteinizing hormone levels decreased with the use of bromocriptine and there was a slight improvement in ovarian function.

D. ANOVULATION AND INFERTILITY

Ovulatory factors account for 27% of the total when considering all the causes of infertility. On the other hand, polycystic ovary syndrome is observed in about 80% of women with anovulatory infertility(9). Even when considered only in terms of infertility, it is seen how important the follow-up and treatment of PCOS is.

This period, which accounts for the majority of female infertility, is usually 6 days for women (10-17 of the menstrual cycle. between the days). Determining this period, is important for knowing the infertile period. For this purpose, we use some tests to detect ovulation;

- Measurement of LH in serum and urine; ovulation occurs approximately 24 hours after evidence of an increase in LH in the urine. Only the pulsatility of LH release complicates the applicability of the test.

- Basal body temperature; in women with an ovulatory cycle, body temperature shows a biphasic pattern and is measured without any physical activity when they wake up from sleep. An average increase of 0.5 degrees may be observed after ovulation. During the luteal phase, an increase in body temperature is observed, and if the body temperature is high for 3 consecutive days, the presence of ovulation is indicated.
- Evaluation of cervical mucus; during the fertile period, cervical mucus is slippery and clean. Especially 48-72 hours before ovulation, the amount of cervical mucus increases a lot.
- Midluteal serum progesterone level; in the midluteal phase (cycle 21. on the day or 7 days after the LH peak), progesterone more than 3ng/ml is a finding in favor of ovulation.
- Serial ultrasonographic monitoring; towards the end of the late follicular phase, the dominant follicle, which reaches 21-23 millimeters, ruptures and minimal mai can be monitored in the douglass. Cysts that disappear during serial ultrasonographic follow-ups during the follicular period and their secondary appearance suggest ovulation (Preovulatory follicles can reach a diameter of 19 mm in spontaneous cycles and 25 mm in clomiphene-induced follicles.).
- Endometrial biopsy; here, in case of secretarial endometrial pathology reporting, it is seen that there is a progesterone effect and the presence of ovulation is shown. However, histological evaluation of the endometrium is not safe in

infertile and fertile women. It has negative consequences in the case of an early pregnancy and is currently not used for the detection of ovulation.

Tests that should be requested when researching infertility caused by ovulatory dysfunction;

- Thyroid stimulating hormone (TSH)
- Prolactin (PRL)
- Follicle stimulating hormone (FSH)
- Luteinizing Hormone (LH)
- Oestrogen
- Total testosterone
- Dihydroepiandrostenedione sulfate (DHEA-S)

Hyperprolactinemia, hypothyroidism, hypothalamic hypophyseal disorders (stress, intense exercise, eating disorders ...), anorexia nervosa, primary ovarian insufficiency and adrenal androgen synthesis disorders are included in the differential diagnosis of PCOS.

Although anovulation is considered as the only cause under the heading of PCOS and infertility, implantation failures due to endometrial dysregulation, obesity described in pathophysiology, which leads to increased symptoms of the disease, and Decrement in oocyte quality due to inflammation processes that constantly develop in the ovarian cortex can also be considered among the causes.

E. PCOS AND OVULATION INDUCTION

1. Lifestyle change

In patients with polycystic ovary syndrome, treatment should primarily focus on lifestyle changes. As a result of the increase in peripheral estrogen production in obese women, the negative feed back effect on FSH increases, and the positive feed back effect of estrogen on LH, the increase in androgen production also deepens the clinic of the disease.

The fact that there are numerous studies showing that there is a noticeable improvement in spontaneous ovulation and menstrual cycles by giving 10% of the current weight to obese and insulin-resistant women with PCOS demonstrates the importance of lifestyle changes(10).

A study conducted in 2015 found that patients with PCOS who underwent bariatric surgery had improved ovulation and menstrual cycles, but obstetric complications such as preterm labor and fetal development restriction were found in the pregnancy follow-up of these patients(11).

2. Selective estrogen receptor modulators

Clomiphene citrate is the most common and preferred first choice drug for ovulation induction. Tamoxifen, which is used in the treatment of breast cancer patients, is also included among SERMs Dec, but it is not used with the indication of ovulation induction.

Clomiphene is a SERM that eliminates the negative feed back effect of estrogen on gonadotropins by entering into competitive inhibition with

estrogen receptors in the hypothalamus and pituitary. Stimulation of the ovary begins before ovulation with an increase in the release of gonadotropins, which stimulate follicle development(12).

Your menstrual cycle is 3-5. 50-150 mg/day for 5 days from day one is the standard treatment protocol of clomiphene. If ovulation is not detected at the doses started according to the patient, the dose is increased. Clomiphene resistance is mentioned if ovulation cannot be achieved despite increasing the daily dose of 150 mg. ovulation cannot be achieved in 15-40% of patients despite clomiphene at a dose of 150 mg/day at the end of 3 cycles. Clomiphene resistance is greater in patients with PCOS who are obese, have high insulin resistance, and have increased androgen levels. In patients who cannot menstruate regularly, clomiphene treatment can be started after menstruation is achieved with progesterone support.

11-12 of the cycle in patients undergoing ovulation induction with clomiphene. ovulation can be triggered by subcutaneous hCG injection when a dominant follicle with an average diameter of >18 mm is detected by ultrasonographic evaluation. Here, hCG contributes to the realization of ovulation with an LH-like effect. In this rotation, couples are recommended to have an extreme relationship on the day. ASRM recommends the urinary LH kit first for the follow-up of ovulation. hCG injection is not routinely recommended for serial ultrasonographic evaluation and ovulation. hCG injection has no positive contribution to pregnancies(13).

Ovulation can be detected at a rate of 50%, pregnancy at a rate of 25% and live birth at a rate of 22% during ovulation induction with

clomiphene. Although ovulation is present, the most important reason for low pregnancy and live birth rates is the failure of implantation. Clomiphene causes thinning of the endometrium due to its antiestrogenic effect on the endometrium. This also leads to implantation failure. According to spontaneous conceptions, the rate of multiple pregnancies has increased by 10 times. In particular, although the antimullerian hormone (AMH) level is high and more than one follicle has reached 17-20 mm levels in serial ultrasonographic evaluations, hCG injection causes this condition. Again, there is also an increased risk of ovarian hyperstimulation (OHSS) when induced with clomiphene.

3. Aromatase inhibitors

This group, which inhibits the aromatase enzyme in the last step of estrogen formed by the aromatization of androgens, causes the level of estrogen in the blood to decrease and the pressure on gonadotropins to be lifted.

Aromatase inhibitors are used to induce ovulation. A menstrual cycle lasts 3 to 7 days. The recommended dose of Letrozole for women is 2.5 mg daily for 5 days (2.5 mg daily) between decays. If not ovulate within 5 days of taking Letrozole, you can increase the dose in subsequent cycles and increase the dose to 7.5 mg daily.

Comparison of clomiphene with letrozole in studies conducted, the risk of multiple pregnancies is low in letrozole without multifollicular development due to the fact that its half-life is less compared to clomiphene. Again, in these studies, ovulation success and live

pregnancy rates are higher in the letrozole group(14). However, with the notification of cardiac anomalies and skeletal malformations in the babies of patients using letrozole, its use in ovulation induction has been removed from the prospectus of the drug by the manufacturer. There are also subsequent studies showing that letrozole does not cause congenital anomalies(15).

Negative effects encountered during the use of clomiphene, such as thickening of cervical mucus and thinning of endometrial thickness, are not observed during the use of letrozole.

4. Metformin

Metformin, which increases insulin receptor activity, inhibits glucose reuptake from the liver and glucose absorption from the intestine, also reduces testosterone production by acting on androgen synthesis in teka cells in the ovary. Considering the effects of insulin and insulin-like proteins involved in the pathophysiology of PCOS, studies with metformin have shown that it is more effective in metabolic disorders, ovulation and regularization of menstrual cycles than placebo(16).

In obese, insulin-resistant and androgen-loaded women with PCOS, it has been found that if clomiphene is added to treatment in addition to ovulation induction, it both breaks clom October resistance and increases ovulation success.

Due to the occurrence of gastric side effects in the first use of patients, treatment compliance should be well adjusted. It should be used in tablet form of 850-1000 mg twice a day in patients with good treatment

compliance. In order to increase the success of treatment, it should be started 3 months before ovulation induction.

5. Inositol

Inositol, a member of vitamin B group, is a sugar-alcohol steroisomer molecule that is in the cell membrane structure. While Myo-inositol allows glucose to be taken into the cell, D-Chiro-Inositol allows glucose taken into the cell to be stored as glycogen.

A meta-analysis conducted in 2018 found that Myo-inositol 2 g/day and D-Chiro-Inositol 0.6g/day showed improvement in spontaneous ovulation, menstrual cycle improvement and metabolic changes compared to placebo after use. Again, it has been observed that there is a decrease in fasting insulin levels with inositol, a decrease in HOMA-IR and an increase in SHBG release(17). Despite all these, it has been reported that it has no effect on oocyte quality, embryo quality and clinical pregnancy formation.

6. Laparoscopic Ovarian Drilling (LOD)

Although the surgical method has been used as the first-line treatment method in patients with PCOS for many years, today it is a treatment that has been relegated to the second plan due to a decrease in ovarian reserve and pelvic adhesions.

LOD, which is used in the second-line treatment in clomiphene-resistant cases, gives the same results as other applications. However, it has been observed that the probability of multiple pregnancies in patients with LOD is lower compared to other treatments.

The operation is based on laparoscopically penetrating into the abdomen and opening 4 holes with a depth of 4 mm and a diameter of 4 mm in remote areas in the hilus of the ovary. With the thermal damage caused, it is observed that the androgenic load decreases, inhibin – B decreases, there is a decrease in AMH levels and there is an improvement in the microenvironment of oocytes.

7. Gonadotropins

Another treatment modality used in ovulation induction is gonadotropins. If ovulation cannot be achieved with clomiphene citrate and letrozole, it is used as a second-line treatment. FSH and LH act by playing a fundamental role in follicle development and the selection of the dominant follicle. Here, FSH-LH preparations are available as well as pure FSH preparations for gonadotropin treatment, and pure FSH preparations are preferred for ovulation induction in PCOS patients.

Due to the risks of excessive stimulation and multiple pregnancies in ovulation induction with gonadotropins, low-dose step up treatment protocols are applied. The drug is started at doses of 37.5-75 IU and continued for 7-12 days. If follicle development is observed during follow-up, it is continued at the same dose; however, when follicle development is not monitored, the dose is increased and ultrasonographic follow-up is continued. ovulation is triggered by hCG injection when the follicle exceeding 17 millimeters is monitored. In order to reduce the risk of multiple pregnancy and OHSS, the cycle is canceled in the presence of 3 follicles of 14 mm and above, hCG injection is not performed.

In a study in patients undergoing ovulation induction with gonadotropin in patients with PCOS, the ovarian hyperstimulation rate was reported as 4.6% and the multiple pregnancy rate was reported as 36%(18). For this reason, it is recommended to follow a low-dose protocol to avoid these risks.

F. RESULT

Polycystic ovary syndrome, a metabolic and endocrine disease of the reproductive period, is often encountered with infertility complaints. Lifestyle changes constitute the first step in the treatment of this syndrome, which has anovulation, hyperandrogenism and autophosphorylation disorder in its pathophysiology. In medical treatment, successful ovulation experiences occur with combinations of clomiphene, clomiphene + metformin and letrozole. When clomiphene resistance is involved and ovulation cannot be achieved with first-line treatment, laparoscopic ovarian drilling and gonadotropin treatments come to mind.

Lifestyle changes, medical methods and surgical methods, as well as in vitro fertilization (IVF) treatment should be switched to cases with ovulation failure.

In this process, where there are different treatment protocols and success comes with clinical experience, success is inevitable with the correct diagnosis, ensuring the patient's compliance with treatment, adequate medical equipment and, perhaps most importantly, sufficient clinical experience. It should not be forgotten that each patient should be evaluated in his/her own way and health services should be provided

by methods in which treatment is individualized without going beyond the proven limits drawn by science.

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CHAPTER XIV

IVF TREATMENT IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is an public health issue that characterized with policystic ovaries, ovulatory dysfunction, metabolic abnormalities such as hyperandrogenism and insulin resistance (1). This diagnosis can be accompanied by a range of clinical signs, including obesity and other aspects of metabolic syndrome, mental health issues like anxiety and depression, and sometimes even infertility. It is one of the primary causes of infertility among reproductive aged women due to anovulation (2). PCOS prevalence vary %8-13 depending on the population and the diagnosis criteria used (1) .More than 90% of women with anovulatuar infertility has the endocrine or ultrasound symptoms of PCOS (3).

In women with PCOS serum anti-mullerian hormone (AMH) is elevated, about 2 to 4 fold elevated than normal, which is believed to be involved in the development of PCOS. Women with PCOS and high AMH levels have a higher risk of hyperresponse after ovarian stimulation than women without PCOS(4).

A recent evidence-based guideline for PCOS recommend that the first-line management of medical infertility therapy is oral ovulation induction agents (letrozole after clomiphene citrate with metformin) for women with PCOS and anovulatory infertility. It recommends gonadotrophins for the second-line treatment. If first or second-line induction therapies have failed and there is not spesific in-vitro fertilization (IVF) indication like male factor or tubal factor, IVF can be used for the third-line therapy in PCOS women (5).

IVF is defined as "a series of procedures that involve extracorporeal fertilization of gametes " by the ESHRE and the ASRM. It is a complicated method of overcoming infertility and one of the forms of Assisted Reproductive Technology (ART). The procedure involves oocyte retrieval after ovarian stimulation , in vitro insemination, and transfer the embryo/s to a uterus. The use of IVF for infertility treatment in PCOS has grown exponentially in recent years. IVF is effective in women with anovulatory PCOS and if elective single embryos are transferred, multiple pregnancy risk is reduced.

PRE-TREATMENT EVALUATION

Before an IVF treatment, a proper evaluation should be taken to optimize outcomes in a patient with PCOS like lifestyle modification, cycle preparation and supplements. Pretreatment with metformin, vitamin D should be considered with body mass index (BMI), AMH and vitamin D levels. Different ovarian stimulation and embriyo transfer strategies has improved in the past years (6,7). Selecting the right ovarian stimulation method and triggering method are critical in reducing the risks of the process. If IVF has been planned for infertility with PCOS, patients need to be counselled about cost, availability, and ovarian hyperstimulation syndrome (OHSS) development risk before treatment.

While age is a disadvantage in all etiologies in terms of infertility, in a study; women with PCOS > 35 years of age had a higher cumulative live birth rate compared to controls. This could be related a higher

oocyte reserve and embryos available compared to controls, which compensated for the poor oocyte quality of aged PCOS patients(8).

In overweight and obese women, infertility is more common, and IVF may not be as benefiicial in these women. Weight loss is reported to be useful for infertile PCOS women. A meta-analysis showed that obese women had lower live birth rate after IVF compared to normal weight (9). Overweight or obese women who undergoing IVF in PCOS have increased risk for low embryo implantation rates and live birth, as well as an increased risk for early abortion with a freeze-all approach (10). Obesity may also affect the quality of oocytes and the sensitivity of the endometrium in patients with PCOS. They have also increased risk of anaesthesia and thus may not tolerate oocyte retrieval. However, studies on the effect of weight loss on outcomes in women with PCOS who will undergo IVF are limited. Although there is no consensus on the role of weight loss in PCOS patients, it may be especially important for the implantation.

ADJUNCT MEDİCAL TREATMENTS

Adjunct metformin therapy can be used before and/or while follicle stimulating hormone(FSH) ovarian stimulation to improve clinical pregnancy rates and reduce the chance of OHSS. Metformin use from day of ovarian supression to oocyt retrieval has a higher clinical pregnancy rate (>12 weeks) and lower OHSS (11). If a GnRH agonist protocol at IVF treatment with PCOS has been planned with usage of metformin; the daily dose should be between 1000 to 2500 mg and should be start with the GnRH agonist . Current guideline for IVF in

PCOS patients recommends adjunct metformin therapy in a GnRH-antagonist protocol to reduce risk of OHSS (12). At the last Cochrane review, it has not a certain effect for the risk of OHSS in this patients but it can be recommended for this purpose (13)

In PCOS patients myo-inositol has been studied.A study showed that folic acid combination with myo-inositol improves blastcocyst/embryo formation and pregnancy rates in PCOS patients according to only given folic acid (14). Another study showed that patients treated with both myo-inositol and folic acid need less gonadotrophin for stimulation and has fewer immature oocytes (15). Also a meta-analysis and randomized controlled trial suggest that myo-inositol decreases gonadotropin dose and duration of ovarian stimulation in PCOS patients undergoing IVF and usage with folic acid improves oocyte and embryo quality (16, 17). Inositol, alone or combination with other drugs, should be seen as an experimental treatment for PCOS women with infertility.

STEPS OF IVF

In the first step of IVF treatment, ovarian stimulation with gonadotrophins is used to stimulate the ovaries to produce more mature oocytes and good-quality embryos for transfer. This overian stimulation increases the risk of OHSS(13). The incidence of OHSS in PCOS patients is higher than without PCOS. There isn't single method to prevent this syndrom. It is beneficial to categorize women based on their OHSS risk and individualizing treatments to reduce their risk of developing OHSS. Clinicians can use both AMH and antral follicle

count for preanalyse the risk (18). Strategies to reduce OHSS risk in a IVF treatment are: low dose gonadotropin ovarian stimulation, co-treatment with metformin, GnRH antagonist protocol instead of a gonadotropin agonist, and a GnRH-antagonist trigger istead of standard HCG trigger. Also for that purpose, use of cabergoline are recommended (13,18).

1-Ovulation Induction: When planning IVF with PCOS, the method chosen for ovulation induction is important in terms of complications and results. The most emphasized issue in this regard is which of the GnRH agonist protocol or GnRH antagonist protocol should be preferred.

GnRH antagonists bind to and compete with the GnRH receptors immediately., while GnRH agonists has an indirect suppression effect to the pituitary gland. This helps to overcome the negative effects of the GnRH agonist protocol.

GnRH agonists are added to IVF controlled ovarian stimulation (COS) protocols to prevent an early surge of LH (Luteinizing Hormone) while follicles are immature. However, there are some drawbacks associated with the use of these protocols, such as longer protocol duration, increased risk of ovarian cysts, and hypoestrogenic effects because of the flare-up period(19,20). The risk of OHSS is already high in PCOS women due to increased antral follicles, increased levels of AMH, and estradiol. With the use of an agonist protocol, the COS response will increase, thus OHSS risk will be higher(21). For ovulation induction, lower doses of gonadotropins were needed for PCOS patients. No

significant difference of gonadotropin dosage was detected for studies using GnRH antagonist protocol for induction. Although longer stimulation days for ovarian stimulation were detected at that group(22). A randomized controlled trial suggests that the GnRH antagonist protocol is associated with lower incidence of OHSS, lower gonadotropin doses and shorter duration of stimulation compared to GnRH agonist (23).

A recent meta-analysis compared the GNHR antagonist protocol to the GNHR agonist protocol in PCOS women undergoing IVF. The meta-analysis did not provide sufficient evidence to support a comparison between the two protocols in terms of ongoing pregnancy, live-birth, clinical pregnancy rates per woman and the number of oocytes retrieved . However, the GNRH antagonist protocol was associated with a reduced risk of OHSS. In women undergoing IVF treatment with PCOS, GNRH antagonist protocols are preferred over GNRH agonist protocols and an elective Frozen Embryo Transfer strategy may be considered. Adjunct metformin therapy may be used if the GnRH agonist protocol is used (24). Also in last review it is showed that metformin use with GnRH agonist protocol could increas clinical pregnancy rate(CPR) and has not certain effect on live birth rate. On the other hand, usage with GnRH antagonist protocol could reduce live birth rates and has not certain effect on CPR(5).

2-Oocyte Maturation Trigger : After ovarian stimulation and achieved sufficient mature oocytes, following thing is to choose the trigger. HCG with similarities with LH has been used as a alternate for the endogenous LH surge in IVF cycles. Due to its flare effect, GnRHa has

used as an alternative trigger for releasing pituitary endogenous gonadotrophins. However, its shortlived LH surge (24-36 h) results rapid luteolysis (25), severe fall of steroid hormones and VEGF. A useful result of VEGF dicrease is lower incidence of OHSS.

GnRH agonist triggers are related to lower pregnancy rate but reduced OHSS risk. It can be differ in fresh or frozen embryo use for transfer. A Cochrane review showed that the use of GnRH agonists for oocyte maturation triggering is is associated with: low ongoing pregnancy rate, low live birth rate, higher miscarriage rate compared to HCG trigger in fresh cycles(26).

In evidence based guideline, if a fresh embryo transfer is not planned or there is a higher risk of OHSS, GnRH agonist trigger and embryo freezing is recommended, in a GnRH antagonist protocol. The trigger choice with GnRH agonist to hCG is an important step to dicrease the risk of OHSS (5).

3-Embryo Transfer : Randomized controlled trials and meta-analyses with PCOS and IVF are limited, and concerns over which technique is safer with IVF are important for women with PCOS. With advances in cryopreservation, Frozen Embryo Transfer (FET) is becoming more popular, and some research has even suggested that FET can lead to better neonatal outcomes. Among women with PCOS, FET was associated with a higher rate of live births, a lower rate of OHSS, and a higher rate of preeclampsia compared with fresh embryo transfer. In addition, there is still a lot of uncertainty regarding the quality of the oocytes and embryos, the implantation rate, the cleavage rate, the side

effects and the common side effects in PCOS women who undergo IVF (12). Although there are studies suggesting that the malformation rate is higher or lower in frozen embryo transfer(27,28), this issue requires more research.

OUTCOMES and COMPLICATIONS

The association between ectopic pregnancy after IVF-ET in PCOS also has been studied. It shows that ectopic pregnancy is higher after controlled ovarian hyperstimulation in fresh ET cycles in PCOS but not in frozen-thawed ET cycles. One possible reason for this is that PCOS women seem to have a lower threshold for the hyperphysiological level of estradiol that causes ectopic pregnancy post-COH compared to non-PCOS women. (29).

When the rates of early pregnancy loss were analyzed for PCOS women undergoing IVF- ET, there were no statistically significant differences compared to IVF-et grup for women without PCOS(30).

Fresh embryo transfer, higher antral folllicle count (AFC), and high 2nd hour glucose concentration after 75 gr OGTT have related for clinical pregnancy loss in PCOS women. Especially with higher AFC, FET can be a better treatment to decrease pregnancy loss. For those who have FET, 2nd hour glucose concentration is related to clinical pregnancy loss so they should have close monitoring(31).

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CHAPTER XV

PREGNANCY OUTCOMES IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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INTRODUCTION

Significant multisystem reproductive, metabolic, and psychological effects are caused by polycystic ovarian syndrome. (Teede, Deeks, & Moran, 2010) Infertility and poor pregnancy outcomes are reproductive manifestations. Metabolic risk factors for polycystic ovarian syndrome are cardiovascular diseases, type 2 diabetes mellitus and obesity. (Conway, Dewailly, & Diamanti-Kandarakis, 2014) Anxiety, depression and also low quality of life are psychological elements. (Teede, Deeks, & Moran, 2010) According to twin studies, polycystic ovarian syndrome can be passed down to future generations by up to 70%, is associated with certain genetic abnormalities, and can have serious negative consequences on the offspring of afflicted women. (Hayes , Urbanek, & Ehrmann, 2015) (Davies, Marino, & Willson, 2011) These are important areas for improving health and are the primary causes of disease burden for women of all ages. It's crucial to remember that PCOS affects women differently, making them more vulnerable to the metabolic and reproductive issues that come with puberty. Numerous investigations into the possibility of pregnancy problems in PCOS have been conducted. Pregnancy in women with PCOS may be classified as high-risk and necessitate increased prenatal care because of polycystic ovarian syndrome and its characteristics. Endocrine diseases, diabetes, obesity, repeated pregnancies, and a history of unfavorable pregnancy outcomes are some of these symptoms. Although this is the case, PCOS is not a factor evaluated in normal prenatal screening to detect high-risk pregnancies. (Brown, Lindheimer, & Swiet, 2001) According to the guidelines of the Endocrine Society, in case of pregnancy planning for women diagnosed

with Polycystic Ovary Syndrome, blood pressure and body mass index should be checked in the preconceptional period and oral glucose screening test is recommended. (Legro, Arslanian, & Ehrmann, 2013) According to the results obtained, we can say that the pregnancies of women with polycystic ovary syndrome have a worse prognosis.(Boomsma, Eijkemans, & Hughes, 2006) (Yu, Chen, & Rao, 2016)

MATERNAL ADVERSE PREGNANCY OUTCOMES

Inconsistent data points to a higher incidence of miscarriage in PCOS-positive women. According to the most current meta-analysis, women with PCOS have a 2.9-fold greater risk of miscarriage than women without the condition. (Yu, Chen, & Rao, 2016) However, even among the studies that enrolled women from infertility treatment centers, the outcomes varied depending on the research design. The confounding effects of body mass index and assisted reproductive technologies, which may increase miscarriage and are commonly disregarded in statistical analysis or research design, are significant obstacles. (Yu, Chen, & Rao, 2016) In prospective studies, the risk of abortion increased 2-4 times in people who were diagnosed with PCOS and became pregnant compared to the control group (pregnant women without PCOS).(Elkholi & Nagy, 2014) (Wang, Dai, & Yang, 2016) In PCOS-afflicted women, hyperinsulinemia and hyperandrogenism may interfere with normal placental implantation, which may lead to pregnancy loss. (Al-Biate, 2015) However, more extensive prospective studies are required that take additional maternal and fetal factors for pregnancy loss into account. With different screening procedures,

timing for measurements, and suggested glucose cut-offs, gestational diabetes is a difficult pregnancy outcome. Different nations use criteria that have changed over time for screening for gestational diabetes. There is no clear glucose cut-off value for adverse pregnancy outcomes in pregnant women with PCOS, but a correlation was found between persistently high blood glucose values and poor pregnancy prognosis in these patients. (Farrar, Duley, & Lawlor, 2011) However, aggregate meta-analyses to date show that women with PCOS are at considerably greater risk for gestational diabetes than women without PCOS (range from 2.8 to 3.7). (Boomsma, Eijkemans, & Hughes, 2006) (Yu, Chen, & Rao, 2016)

Women with and without PCOS follow the same procedure in nations where screening is mandatory. PCOS status must be included together with other characteristics including ethnicity, a positive family history, and body mass index if risk-based screening is employed, such as under the NICE (National Institute for Health and Clinical Excellence) guidelines (Farrar, Duley, & Lawlor, 2011) Also three to four times more likely to get preeclampsia and gestational hypertension during pregnancy are women with polycystic ovarian syndrome. (Kjerulff & Sanchez-Ramos, 2011) (Qin , Pang, & Li, 2013) Gestational hypertension was noted in 12.7% and 5.3% of singleton pregnancies in a study including 150 women with PCOS who were diagnosed using the Rotterdam criteria and 150 controls without PCOS (P =.042). (Palomba, Falbo, & Chiossi, 2014) The ICD-10 classified healthy controls and women with PCOS who visited a private fertility clinic were chosen from the same birth cohort for the study. The findings

demonstrated that gestational hypertension was equally less common in women with and without polycystic ovarian syndrome. (1% vs. 2%; P =.457). (Naver , Grinsted, & Larsen, 2014) The presence of PCOS was not expressly eliminated among the controls, though. Pre-eclampsia has also been discovered to occur more frequently in women with polycystic ovarian syndrome. (odds ratio: 3.5; 95% confidence interval (CI): 1.9-6.2). (Boomsma, Eijkemans, & Hughes, 2006) Despite having a uniform definition across all trials, pre-eclampsia risk in multiple pregnancies was either the same as in singleton pregnancies or much greater in both cases. (Lovvik, Wikstrom, & Neovius, 2015) (Doherty, Newnham, & Bower, 2015) It is known that hypertensive diseases of pregnancy are more common in multiple pregnancies. Pregnancy complications have increased in pregnant women with PCOS due to increased multiple pregnancy rates compared to the normal population. (Qin , Pang, & Li, 2013) Overall, further investigation is required to ascertain if polycystic ovarian syndrome raises the risk of hypertensive problems during pregnancy. It is seen that cesarean section rates are higher in pregnant women with PCOS. (odds ratio: 1.2; 95% CI: 1.1-1.7). (Yu, Chen, & Rao, 2016) In both investigations, the mean newborn birthweight was comparable between groups. Contradictory findings, however, may have been caused by variations in PCOS diagnosis standards and caesarean delivery reasons among research participants. (Kollmann, Klaritsch, & Martins, 2015) In studies examining pregnancy outcomes, PCOS and its components have been diagnosed in various ways, as shown in **Figure 1.**

Figure 1: Diagnosis of Polycystic Ovarian Syndrome in studies evaluating pregnancy problems in PCOS-affected women. BMI (body mass index), FSH (follicle stimulating hormone), LH (luteinizing hormone), SHBG (sex hormone binding globulin), HOMA-IR (Homeostatic Model Assessment for Insulin Resistance)

FOETAL AND INFANT COMPLICATIONS

PCOS-related risk factors may combine with maternal pregnancy problems to worsen the outcomes for the fetus and the newborn. According to meta-analyses, children of moms with PCOS often arrive to the hospital earlier than children of mothers without PCOS. (Boomsma, Eijkemans, & Hughes, 2006) (Yu, Chen, & Rao, 2016) However, whether preterm delivery was induced or spontaneous is typically not mentioned in these research. (Boomsma, Eijkemans, & Hughes, 2006) It might be challenging to tell whether a premature delivery that has been prescribed by a doctor because of a fetal or maternal illness is the primary reason of preterm birth.

Animal studies indicate that hyperandrogenism may impair fetal development; but, if it coexists with insulin resistance or hyperinsulinemia, it may instead enhance fetal size. (Sir-Petermann & Hitchsfeld, 2005) (Mumm, Jensen, & Sorensen, 2015) On the other hand, persistent hyperinsulinemia can impede fetal development by disrupting vascular function. (Bennett, Tita, & Owen, 2015) This might lead to inconsistent outcomes since different research utilize different cut-off points to define hyperandrogenism and hyperinsulinemia. A study comprising 400 obese mothers with and without PCOS and matching age and BMI found no fetuses with intrauterine growth limitation. (Elkholi & Nagy, 2014) In contrast to controls with a comparable age and BMI, Wang et al. found that intrauterine growth restriction was more common in PCOS-positive women. (Wang & Zhao, 2013) Despite inconsistent findings in individual research, meta-analyses have revealed comparable risks for small for gestational age birth among children delivered to women with and without PCOS. (Boomsma, Eijkemans, & Hughes, 2006) (Yu, Chen, & Rao, 2016) (Nouh & Shalaby, 2011) (Palomba, Falbo, & Chiossi, 2014) The chance of having a baby that is big for gestational age does not seem to be significantly affected by PCOS. (Naver , Grinsted, & Larsen, 2014) (Wang & Zhao, 2013) Given the pathophysiology of PCOS's underlying effects of hyperinsulinemia and obesity and the increased risk of gestational diabetes among women with PCOS, a higher risk for large for gestational age births can be anticipated among these women. (Stepto, Cassar, & Joham, 2013) (Yu, Chen, & Rao, 2016) The contrary outcomes can serve as a reminder of the significance of taking lifestyle variables into account, since doing so can help PCOS-affected

women with hyperandrogenism, obesity, and insulin resistance. (Lim, Davies, & Norman, 2012)

According to meta-analyses, children delivered to women with PCOS are more likely to require admission to a neonatal intensive care unit as a result of a more problematic pregnancy (OR: 2.3; 95% CI: 1.4-3.8). (Boomsma, Eijkemans, & Hughes, 2006) (Qin , Pang, & Li, 2013) The likelihood of admission to a newborn intensive care unit is increased by the higher prevalence of prematurity and illnesses connected to it, such as respiratory distress syndrome. (Fridstrom, Nisell, & Sjoblom, 1999) While a research that looked at neonatal intensive care unit admissions by the cause for admission found no difference in risk between women with and without PCOS, Bjercke et al. observed increased neonatal critical care unit admission rates for children born to mothers with PCOS. However, they suggested that these findings may be explained by routine admission of children delivered to moms who had gestational diabetes, which was more common in PCOS-affected individuals. (Turhan, Seckin, & Aybar, 2003) (Bjercke, Dale, & Tanbo, 2002)

Due to the increased probability of multiple pregnancies and preterm birth, it has also been observed that infants born to moms with PCOS are at a greater risk of perinatal death. (Boomsma, Eijkemans, & Hughes, 2006) Additionally, we point out that earlier meta-analyses that revealed an elevated risk of perinatal death for children of women with PCOS included a research that reported results in women who had several pregnancies throughout the study period, as opposed to the

women in other studies who had only one. (Boomsma, Eijkemans, & Hughes, 2006) (Yu, Chen, & Rao, 2016) (Mikola, Hiilesmaa, & Halttunen, 2001) In subsequent pregnancies, there is a substantial likelihood that pregnancy problems may return. (Roos, Kieler, & Sahlin, 2011) As a result, this heterogeneity could have an impact on the reported elevated ORs in these meta-analyses.

POSSIBLE MECHANISMS FOR PCOS TO PLAY A ROLE IN UNFAVORABLE PREGNANCY OUTCOMES

It is therefore plausible that unfavorable pregnancy outcomes in PCOS may vary according to diagnostic criteria given the link between obesity, insulin resistance, and pre-existing metabolic problems with poor pregnancy outcomes in women in the general population. There isn't much study looking into this theory. According to some studies, a combination of hyperandrogenism, insulin resistance, and/or hyperinsulinemia may increase a woman's risk of experiencing negative pregnancy outcomes, such as pregnancy loss, fetal growth abnormalities, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, and antepartum hemorrhage. (Al-Biate, 2015) (Sir-Petermann & Hitchsfeld, 2005) (Mumm, Jensen, & Sorensen, 2015) (Lovvik, Wikstrom, & Neovius, 2015) (Falbo & Palomba , 2014) (Teede, Misso, & Deeks, 2011)

Insulin resistance: It has been demonstrated that insulin affects blood vessels directly and indirectly, causing vasoconstriction and hypertensive problems during pregnancy. (Aktun, Yorgunlar, & Acet, 2016) By stimulating numerous growth factors, insulin also encourages

prothrombotic and profibrotic actions. (Zhou, Schulman, & Zeng, 2012) The blood pressure response to salt ingestion may be enhanced by hyperinsulinemia. (Zhou, Schulman, & Zeng, 2012) Additionally, it has been discovered that insulin resistance itself raises the risk of pre-eclampsia and gestational hypertension. (Bjercke, Dale, & Tanbo, 2002) Poor perinatal outcomes are linked to the presence of vascular disorders, including an increased risk of preterm birth, caesarean section, perinatal death, and growth disorders in the developing baby, which lead to births that are smaller for gestational age and larger for gestational age. (Bennett, Tita, & Owen, 2015) This highlights how critical hyperinsulinemia is in the development of poor pregnancy outcomes in PCOS-affected women.

BMI and gestational weight gain: According on evidence from combined meta-analyses, up to 61% of women with PCOS are thought to be overweight or obese. (Lim, Davies, & Norman, 2012) According to Yu et al.'s comprehensive review and meta-analysis, the link between PCOS and adverse pregnancy outcomes may vary depending on prepregnancy BMI. (Yu, Chen, & Rao, 2016) BMI has an impact on a woman's likelihood of developing GDM and dysglycemia if she has PCOS, with a BMI over 25 kg/m2 being a significant indicator of GDM. (Turhan, Seckin, & Aybar, 2003) In a case-control study of 1360 women with GDM, Aktun et al. found that women with PCOS had significantly higher mean gestational weight gains at 24-28 weeks of pregnancy and at birth. (Aktun, Yorgunlar, & Acet, 2016) The prevalence of GDM in all women and the higher prepregnancy BMI in PCOS-positive women (22.9 1.9 vs 21.4 1.9 kg/m2) were potential

confounding variables. Similar pre-pregnancy BMI and gestational weight growth were observed by Palomba et al. (Russo, Palomba, & Falbo, 2012) Studies have shown mixed results about how much weight women with PCOS acquire during pregnancy. It is also unclear how gestational weight increase influences negative pregnancy outcomes in women with polycystic ovarian syndrome given the unequal gestational weight gain findings and the lack of correction for any potential confounding effects of gestational weight rise on pregnancy outcomes.

Inflammation : In PCOS, low-grade chronic inflammation may be brought on by hyperandrogenism, insulin resistance, and/or inflammatory cytokines like IL-6 and IL-8, as well as cellular adhesion molecules like soluble endothelial leucocyte adhesion molecule-1, soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule- 1. (Lovvik, Wikstrom, & Neovius, 2015) (Wang & Zhao, 2013) (Diamanti-Kandarakis & Paterakis, 2006) On the other hand, natural physiological changes during pregnancy include the aberration of the mother's immune system, which has resulted in a raised WBC count and CRP levels. (Falbo & Palomba , 2014) Women with PCOS have increased blood levels of WBC and CRP before getting pregnant, according to a prospective research by Palomba et al. These elevations during pregnancy are also significantly higher and are linked to adverse maternal and neonatal outcomes, including gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, antepartum hemorrhage, small for gestational age birth, and large for gestational age birth. (Lovvik, Wikstrom, & Neovius, 2015) (Falbo & Palomba , 2014) (Wolf, Sandler, & Hsu, 2003). It is unclear what

causes inflammation to contribute to unfavorable pregnancy outcomes, especially in PCOS.

Infertility and multiple pregnancy : Although approximately 74% of women with polycystic ovary syndrome can become pregnant spontaneously, the rate of referral to a physician due to infertility is still 76%. (Hudecova, Holte, & Olovsson, 2009) It's crucial to take into account how infertility and assisted reproductive technologies may affect PCOS-afflicted women's ability to get pregnant. Preterm delivery, low birthweight, congenital abnormalities, gestational diabetes, and hypertensive problems during pregnancy are among the negative pregnancy outcomes that infertility or subfertility itself has reportedly been connected to, even in spontaneously conceived pregnancies. (Zhu, Obel, & Bech, 2007) (Basso, Obel, & Zhu, 2006) The use of assisted reproductive technology has been linked in several systematic evaluations to increases in a variety of undesirable pregnancy outcomes. This was supported by a recent comprehensive review of 52 cohort studies from throughout the world that compared singleton births achieved with assisted reproductive technology against spontaneous conception. They showed considerably higher pooled estimates for pregnancies resulting from the use of assisted reproductive technology for all outcomes taken into account, including preterm birth (10.9%, 95% CI 10.0-11.8) and extremely preterm delivery (32 weeks gestation). Low birthweight (2500 g), 2.4% (95% CI 1.9-3.08) 8.7% (95% CI 7.4-10.2), very low birthweight (less than 1500 g) 1.1% (95% CI 0.9-1.3), perinatal mortality 2.0% (95% CI 1.5-2.6), small for gestational age birth 7.1% (95% CI 5.5-9.2), and

congenital abnormalities 5.7% (95% CI 4.7-6.9). (Qin, Wang, & Sheng, 2016) It should be highlighted that some of the underlying causes of issues in fetuses and infants are likely shared by infertility and problems with mother's pregnancy. (Boomsma, Eijkemans, & Hughes, 2006) (Basso, Obel, & Zhu, 2006) (Zhu, Obel, & Bech, Infertility, infertility treatment and fetal growth restriction., 2007)

In the order of choice for ovulation induction, letrozole, clomiphene citrate (with or without metformin), and gonadotropins are recommended for treating anovulatory infertility in women with polycystic ovarian syndrome. These medications may cause ovarian hyperstimulation syndrome, multiple pregnancies, or gastrointestinal problems. (Teede, Misso, & Deeks, 2011) (Legro, Arslanian, & Ehrmann, 2013) The complexity is heightened by the fact that multiple pregnancies increase the risk of adverse pregnancy outcomes, such as preterm birth and low birthweight, and that multiple pregnancies are typically more prevalent in women who use assisted reproductive technology to conceive a child, though there is significant geographic variation. (4%–27%). (Kushnir, Barad, & Albertini, 2017) According to studies by Lvvik et al. on twin pregnancies in women with and without polycystic ovarian syndrome, women with polycystic ovarian syndrome had a larger risk of preterm delivery and extremely preterm birth, but not low birthweight. (Lovvik, Wikstrom, & Neovius, 2015) Recent research on dichorionic diamniotic twin pregnancies has shown that these multiple pregnancies are more likely to result in unfavorable pregnancy outcomes like placenta praevia, preterm birth, very preterm birth, low birthweight, and congenital malformations than

single pregnancies. (Qin, Wang, & Sheng, 2016) As a result, pregnancies in infertile or subfertile women with PCOS are associated with a higher risk of adverse outcomes, which may be exacerbated by factors including infertility treatment and multiple pregnancies.

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CHAPTER XVI

MENTAL HEALT AND STRESS IN POLICISTIC OVARY SYNDROME

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the leading endocrine disorder diagnosis among women of reproductive age globally. PCOS impacts around 5-15% of females worldwide(Agrawal et al., 2004). Polycystic ovary syndrome (PCOS) is characterized by the presence of hyperandrogenism, chronic anovulation, and the detection of polycystic ovaries through ultrasound examination(ESHRE & Group, 2004). Polycystic ovary syndrome (PCOS) can be diagnosed through meeting at least two of three criteria. Numerous hypotheses address the etiology of PCOS, with many complementing one another. The most commonly acknowledged theory states that insulin resistance and hyperinsulinemia lead to hyperandrogenism, causative factors in the development of PCOS. Of late, the prenatal exposure to increased androgen levels hypothesis has gained significant traction within the academic community(Franks & Berga, 2012). The significance of epigenetic factors in the emergence of PCOS in adolescence and adulthood is highlighted. PCOS development could also be attributed to a genetic disorder, possibly involving gene polymorphisms. Women with PCOS have been observed to have higher prevalence of different psychiatric disorders, although the number of studies conducted on this is still limited. Women with PCOS are more likely to experience certain conditions compared to the general population. These conditions include anxiety and depression, eating disorders, obsessive-compulsive disorder, and attention deficit hyperactivity disorder (ADHD). Additionally, bipolar affective disorder, schizophrenia and other psychotic disorders have been reported(Cesta et al., 2016).

Depression

The initial study regarding the correlation between PCOS and depression underwent a pilot-phase at Stanford University. A cohort of 32 women diagnosed with PCOS participated, with 16 of these women also diagnosed with depression. Intriguingly, the incidence of depression was found to be less prevalent among those women who had been prescribed oral contraceptives(Rasgon et al., 2003). In 2007, American gynecologist Anuja Dokras and her team conducted a study in which the diagnosis of depression was made using the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)(Hollinrake, Abreu, Maifeld, Van Voorhis, & Dokras, 2007). A total of 103 women diagnosed with PCOS, along with a control group, were assessed in this study. The prevalence of depression in PCOS patients was found to be 21% in contrast to only 3% in healthy women. The initial meta-analysis in this area took place in 2011 and investigated 17 papers comprising 522 PCOS patients and 475 controls. (Dokras, Clifton, Futterweit, & Wild, 2011). The 2015 study released by the Department of Infertility and Reproductive Endocrinology at Poznan University of Medical Sciences found a four-fold increase in depression prevalence among women diagnosed with polycystic ovarian syndrome. These findings were based on a meta-analysis of existing research. The 2015 study released by the Department of Infertility and Reproductive Endocrinology at Poznan University of Medical Sciences found a four-fold increase in depression prevalence among women diagnosed with polycystic ovarian syndrome. (Głowińska, Zielona-Jenek, Pawelczyk, & Banaszewska,

2016). A cohort of 84 patients diagnosed with PCOS were recruited to take part in the study by completing the Beck Depression Inventory questionnaire. More than half (52%) of the participants displayed signs of depression, within which 32 women reported mild symptoms, 8 reported moderate symptoms, and 2 reported severe symptoms. The study was conducted in 2015 by Greenwood et al. (Greenwood, Pasch, Shinkai, Cedars, & Huddleston, 2015) A total of 301 women with PCOS were evaluated in a cross-sectional study, where the results indicated that 44% of these women were at risk for depression on the Beck Depression Inventory Fast Screen (BDI-FS). The study revealed significant correlations between depression, insulin resistance (HOMA-IR), and BMI. (Greenwood et al., 2015). In a retrospective cohort study based on the population, which was conducted in 2015, Hart and Doherty [10] analysed a large sample consisting of 25,660 women randomly selected and matched by age, without a PCOS diagnosis, and 2,566 polycystic ovary syndrome patients who had been admitted to the hospital between 1997 and 2011. The study revealed a greater prevalence of comorbidities among individuals with PCOS compared to those without the condition. Specifically, individuals with PCOS displayed higher rates of diabetes (12.5% vs 3.8%), obesity (16.0% vs 3.7%), hypertension (0.8% vs 0.2%), asthma (10.6% vs. 4.5%), and depression (9.8% vs. 4.3%). Cesta et al. [8] carried out a comprehensive study using Swedish national registers to investigate the link between psychiatric comorbidity and PCOS. A total of 243,850 controls and 24,385 patients with PCOS were evaluated. The study indicated that women with PCOS have a significantly higher likelihood of developing depression, including severe depression. The most recent

meta-analysis of eleven studies supports these findings. (Cooney, Lee, Sammel, & Dokras, 2017). The meta-analysis revealed that women with PCOS had nearly four times as many symptoms of depression, regardless of severity (the odds ratio (OR) was 3.78). An study of 18 research on the co-morbidity of moderate and/or severe depression revealed that women with PCOS had a four-fold greater risk of depression (OR of 4.18). (Cooney et al., 2017). 958 Daniel Rodriguez-Paris et al.

Anxiety disorders

The State-Trait Anxiety Inventory (STAI) questionnaire, which differentiates between state anxiety (STAI-S) and trait anxiety (STAI-T), is a commonly adopted diagnostic tool for assessing anxiety disorders. In 2011, a study of 130 PCOS patients evaluated their hormonal and metabolic profiles and anxiety levels via the STAI-T and STAI-S inventories.(Livadas et al., 2011) Participants with higher STAI-S and STAI-T scores showed higher insulin resistance, while females with higher STAI-T scores also showed increased resistance. As per Dokras et al. (Dokras, Clifton, Futterweit, & Wild, 2012) published a meta-analysis on the association of PCOS with anxiety (Dokras et al., 2012). The prevalence of generalized anxiety disorder was evaluated in four studies meeting the criteria. Results showed that patients with PCOS had considerably higher rates of the disorder in comparison to controls (8 out of 204, 3.9% vs. 42 out of 206, or 20.4%). The study conducted by Gowiska et al. [8] in 2016 examined the factors influencing emotional difficulties and mood disorders in women affected by PCOS. The study measured an average STAI score

of 42.88, with a standard deviation of 10.35 (measured scores ranged from 21 to 69). The score equates to a STEN score of 7 (standard ten), indicating the mean anxiety levels for the Polish population. (Głowińska et al., 2016). A 2015 study conducted in Australia revealed a greater occurrence of anxiety disorders (14.0% versus 5.9%) in a substantial pool of PCOS patients when compared to a control group. (Hart & Doherty, 2015). The study conducted by Cesta et al. [8] indicated that women diagnosed with PCOS exhibited a higher prevalence of anxiety disorders, specifically generalized anxiety disorder, which was 58% more frequent.(Cesta et al., 2016). The prevalence of social phobias among patients with PCOS was 43% higher than in the general population. Likewise, obsessive-compulsive disorder was also found at a higher rate of 37%. As per the recent meta-analysis by Dokras et al., women having PCOS have a six-fold increased rate of anxiety disorders (OR = 5.62) in comparison to the general population, regardless of disease severity.(Cooney et al., 2017).

Sexual dysfunction

Studies on sexual dysfunction have been published less frequently compared to those on depression or anxiety disorders. The phenotypical traits of women with PCOS, including hirsutism, acne, and/or obesity, may impact their emotional states and indirectly affect their sexual function. In 2003, Elsenbruch et al. published their findings from a study with 50 PCOS patients and 50 controls. (Elsenbruch et al., 2003). The study by de Niet et al revealed a significant association between polycystic ovarian syndrome and notable limitations in sexual gratification among women afflicted by it. (De Niet et al., 2010)

Stovall's research on the sexuality of women with PCOS, published in 2012, found a significant association between amenorrhea and low self-esteem, increased social anxiety, and early onset of sexual activity (sexarchy) in 480 women with PCOS. (Lizneva et al., 2016) No evidence of further sexual dysfunction was found. A population study conducted by Cesta et al found that the incidence of gender identity issues was twice as high in women with PCOS compared to those without (OR = 2.02). [4]. The study conducted by Agrawal et al. in 2004 analysed a sample of 618 females (254 identifying as homosexual and 364 as heterosexual) who were referred for intrauterine insemination fertility treatment. (Agrawal et al., 2004). In contrast to 32% of heterosexual women, ultrasonographic imaging revealed that 80% of lesbian women had polycystic ovaries. The study indicated that only 14% of heterosexual women had PCOS, while 38% of homosexual women had the disorder. Furthermore, homosexual women with polycystic ovary syndrome exhibited higher levels of testosterone. The findings from the Epidemiologic Study of Health Risk (ESTHER) project do not provide evidence to support the idea that homosexual women have a higher prevalence of PCOS. The study examined a sample of 114 homosexual women and 97 heterosexual women (Smith et al., 2011).

Attention deficit hyperactivity disorder (ADHD)

At present, there is a lack of substantial literature regarding the occurrence of attention deficit hyperactivity disorder in women who have been diagnosed with polycystic ovary syndrome. A study scrutinised 40 women with PCOS and 40 healthy controls, concluding

that women diagnosed with PCOS evidenced considerably higher scores on the adult ADHD scale. (Hergüner, Erdur, Başçiftçi, & Herguner, 2015) . It was found that the PCOS group had a greater incidence of childhood ADHD than the control group, based on the Wender-Utah Rating Scale (Rodriguez-Paris et al. 960, Autism). The correlation theory linking elevated androgen levels with autism proposes that women with PCOS may be more susceptible to the condition (Ingudomnukul et al.).

The study results revealed that the PCOS group had a higher incidence of childhood ADHD than the control group as determined by the Wender-Utah Rating Scale (960 Daniel Rodriguez-Paris et al., Autism). It has been suggested that the elevated androgen levels associated with PCOS may be linked to a higher predisposition to autism among women (Ingudomnukul et al.)(Ingudomnukul, Baron-Cohen, Wheelwright, & Knickmeyer, 2007) The researchers analysed 183 mothers of typically developing children, 74 mothers of autistic children, and 54 mothers of autistic women. They found that women with autism spectrum disorders and mothers of autistic children had a higher incidence of hirsutism, acne, menstrual difficulties, and elevated testosterone levels. In 2016, the results of a Swedish population-based study, which looked at 208,796 healthy controls and 23,748 autistic participants, were published (Kosidou et al., 2016). It has been established that children born to mothers with PCOS have an increased risk of developing autism, irrespective of gender. Cesta et al. [4] conducted a population-based study that revealed the prevalence of autism spectrum disorders to be over twice as high (OR = 2.09), with a

greater incidence of classic autism (57%; OR = 1.57) and Asperger's syndrome (80%; OR = 1.8).

Eating disorders

Eating disorders are more prevalent amongst women suffering from polycystic ovary syndrome.(Ålgars et al., 2014). In a study published in 2017, Cesta et al. [8] found that women with PCOS were 35% more likely to exhibit bulimia (OR = 1.35). The researchers assessed a group of 148 women with PCOS and 106 control participants using the Eating Disorder Examination Questionnaire (EDE-Q). (Lee et al., 2017) It has been shown that patients with PCOS, especially those who additionally experience anxiety, regardless of their body mass, are significantly more likely to receive anomalous EDE-Q scores.

Bipolar disorder

There is limited, inconclusive research on the relationship between bipolar affective disorder and PCOS. However, evidence suggests a greater incidence of polycystic ovary syndrome (PCOS) in women with epilepsy or bipolar disorder who are treated with valproate (VPA). (Bilo & Meo, 2008). The findings of these studies were inconclusive and failed to establish any clear correlation. Klipstein and Goldberg carried out the initial pilot investigation in 2006 to explore the potential correlation between PCOS and bipolar disorder.

(Klipstein & Goldberg, 2006). 78 female patients diagnosed with PCOS were screened using the Mood Disorders Questionnaire (MDQ). It was observed that 28% had previously been diagnosed with bipolar disorder or met the diagnostic criteria. An Iranian case-control study was

conducted on 110 women with PCOS and an equal number of age-matched infertile women.

(Davari-Tanha, Rashidi, Ghajarzadeh, & Noorbala, 2014). Whilst 8% of the PCOS group received a diagnosis of bipolar disorder, no such diagnosis was observed in the control group. Surprisingly, the prevalence of depression was found to be higher in the control group in this study.

On the contrary, the cohort study "Psychiatric disorders in women with polycystic ovary syndrome" (961 participants comprising of 5,431 patients with PCOS and 21,724 controls), published by Hung et al in 2014, did not corroborate a greater occurrence of bipolar affective disorder in the PCOS cohort.(Hung et al., 2014). The most extensive study of psychiatric disorders in women with PCOS was conducted by Cesta et al [4]. They discovered a 91% higher average prevalence of bipolar affective disorder in women with PCOS (OR = 1.91).

Schizophrenia

In 2011, a systematic review of 96 articles investigating the similarities in the pathogenesis of schizophrenia and polycystic ovary syndrome demonstrated that insulin resistance and elevated testosterone levels were influential factors in the concurrent existence of both conditions. (Matevosyan, 2011). A study conducted in Sweden (OR = 1.82) also found that the prevalence of schizophrenia was 82% greater in women with PCOS. (Cesta et al., 2016)

Recapitulation

The heightened incidence of mental disorders in PCOS patients presents challenges for unequivocal interpretation. It is believed that prenatal excessive androgen exposure may adversely impact brain development, leading to alterations in brain circuitry and abnormal responses to steroid hormones.(Moore & Campbell, 2017). During critical developmental stages, heightened exposure to androgens in female specimens may lead to the masculinization of their brains and, consequently, their behaviour. This phenomenon has been demonstrated in animals. (MacLusky & Naftolin, 1981; Wallen, 2005). Androgen receptors are present in the perinatal and early postnatal female brain (Brock, De Mees, & Bakker, 2015; Mogi, Takanashi, Nagasawa, & Kikusui, 2015). It is plausible that hyperandrogenism and accompanying somatic symptoms, including acne, deep voice, hirsutism, male pattern baldness, and short stature, heighten the incidence of psychiatric complications - particularly anxiety and depression - in people affected by PCOS. Such symptoms are certainly stigmatising for females while having an adverse impact on their quality of life. Post-menopausal androgen treatment has been associated with augmented sexual function. (Somboonporn, Bell, & Davis, 2005). Insulin resistance and obesity have been found to be linked to psychiatric disorders in women with PCOS. This could be due to chronic inflammatory states that cause an increase in levels of pro-inflammatory cytokines, which can worsen symptoms of depression and anxiety. (Krishnadas & Cavanagh, 2012). The third PCOS Consensus Workshop took place in Amsterdam in October 2010. Its

purpose was to consolidate current knowledge and identify gaps in research on several health matters that affect women with PCOS. One of the topics presented was the quality of life (QoL) of PCOS-positive patients. Among the issues debated, one concerned the possible link between the syndrome or its symptoms (such as obesity, hirsutism, infertility, etc.) and the higher prevalence of psychological complications. A study conducted by Greenwood et al. in 2018 discovered a substantial and autonomous connection between insulin resistance and depression in individuals with PCOS. (Greenwood et al., 2018). A three-phased study conducted by ZareMobini et al. [36], involving a multidisciplinary team to analyze results, has concluded that it may be crucial and economical to design a program that primarily concentrates on enhancing the psychological wellbeing and overall quality of life of PCOS patients. It is suggested that scheduling regular appointments with psychologists could be an effective measure in identifying potential psychiatric illnesses, especially in patients who have recently been diagnosed.

Therefore, a comprehensive approach may offer benefits for treating individuals with polycystic ovary syndrome.

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CHAPTER XVII

PCOS AND SEXUAL FUNCTION

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Polycystic ovary syndrome (PCOS) is a multisystemic disease seen in 5-10% of women. It affects many systems due to hyperandrogenism. In addition to endocrinologic and metabolic consequences, women with PCOS have been reported to have decreased self-esteem due to body image disorders. Contrary to popular belief, the center of sexuality is the brain, which causes disruptions in the individual's physiological response to sexuality due to both physical changes and emotional differences in patients with PCOS, leading to sexual dysfunctions.

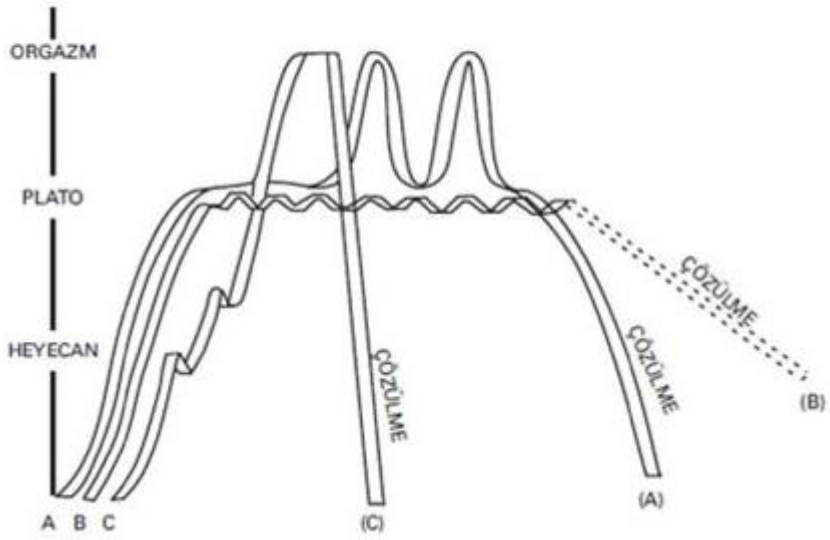

Table 1: Sexual Response Cycle in Women

1. Cycle: arousal phase It is characterized mainly by the emergence of erotic feelings and thoughts, erection in the male, vasocongestion and myotonia in the female. It may occur with any physical or psychological stimulus. Depending

on the duration and intensity of the sexual stimulus, the intensity of the reaction increases rapidly or slowly.

2. Cycle: The plateau phase is part of and a continuation of the arousal phase, during which the feeling of pleasure and sexual tension gradually increases and lasts until the person reaches orgasm. It is the entrance to the orgasm phase
3. Cycle: The orgasmic phase is the shortest in duration but the most intense in terms of the sexual pleasure experienced sensation in the pelvis. Orgasm is concentrated in the clitoral area and vagina in women and in the penis and prostate in men.
4. Cycle: The dissolution phase is characterized by the disappearance of the physiological changes in the genitals and the body as a whole that have occurred in the previous phases in the same sequence over a period of minutes following orgasm or, in the absence of orgasm, a plateau.

Sexual dysfunctions are grouped as vaginismus, decreased sexual desire, dyspareunia, premature ejaculation, orgasm disorder, sexual arousal disorder and sexual aversion disorder.

	Cinsel işlev bozukluğu	Yaşam boyu prevalans %
KADINLARDA	Cinsel istek azlığı	27 - 33
	Uyarılma bozukluğu	10 - 18
	Orgazm bozukluğu	5 - 25
	Disparoni-Vajinismus	3 - 11

Table 2: Prevalence rates of various sexual dysfunctions

In the study conducted by Korkmaz et al, the rate of low self-esteem was higher in women with acne and hirsutism (p=0.014 and p=0.023, respectively). Sexual dysfunction was detected in 47% of women with PCOS who participated in the study. Sexual reluctance due to physical changes caused by PCOS and hirsutism is the most important part of sexual dysfunction(1).

In a meta-analysis of 28 observational studies conducted by Loh et al., it was reported that women with PCOS were 30% more risky than the normal population in terms of female sexual dysfunction.(2) In another study, it was reported that female sexual dysfunction in Malaysia was between 5.5% and 11.2%, and this rate increased up to 62.5% in women with PCOS(3).

In a study by Kölükçü et al, sexual dysfunction was found in 63.3% of women with PCOS (4).

Contrary to this information, there are also studies indicating that sexual function is not negatively affected in women with PCOS. In the study of Diamond et al. no statistically significant sexual dysfunction was detected in women with PCOS(5)

In a meta-analysis conducted by Zhao et al., it was reported that there was no direct relationship between PCOS and female sexual dysfunction.(6) In another meta-analysis, Pastoor et al. found that women with PCOS had a deterioration in their physical attractiveness and negatively affected their sexual life, while their feelings of sexual satisfaction remained similar to the normal population(7).

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CHAPTER XVIII

PCOS AND METABOLIC SYNDROME

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The most prevalent type of anovulatory infertility is polycystic ovarian syndrome. (Frank, 1995, s. 333:853-61.) Many affected women of reproductive age visit a gynecology or infertility clinic because of its link to menstruation disturbance and changed hormonal parameters. Although the exact cause of the syndrome is uncertain, recent research indicates that insulin resistance may be the primary underlying issue, with hyperinsulinemia from the resulting condition promoting excessive ovarian androgen production. These women have a typical dyslipidemia and an increased chance of acquiring cardiovascular disease and non-insulin dependent diabetes later in life due to the widespread insulin resistance. Therefore, it appears that the metabolic syndrome shares many characteristics with polycystic ovarian syndrome. (Talbott, ve diğerleri, 1995, s. 15:821-6.) (Dahlgren , Janson, Johansson, Lapidus, & Oden, 1992, s. 71:599-604.) (Conway, Agrawal, Betteridge, & Jacobs, 1992, s. 37:119-25.)

Dyslipidemia, which frequently occurs in PCOS, typically manifests as raised triglycerides and inadequate HDL cholesterol levels. Dyslipidemia has numerous root causes, and they don't appear to be affected by body mass index. The pathogenesis of dyslipidemia in PCOS involves insulin resistance, which eventually impacts the production of lipoprotein and hepatic lipase as well as the stimulation of lipolysis.

The most significant factors contributing to aberrant glucose metabolism in PCOS are insulin resistance, significantly decreased insulin production, decreased hepatic insulin extraction, poor hepatic gluconeogenesis suppression and irregular insulin receptor signaling.

Approximately 50% to 80% of PCOS women have insulin resistance. Lean women experience less severe insulin resistance than fat women. IGT and type 2 diabetes (DM2) are more likely to occur in women with PCOS than in women who are age- and weight-matched and have normal hormone levels. IGT and DM2 are present in 31.3% and 7.5%, respectively, of PCOS women.There has been inconsistent reporting of the rate of conversion from IGT to DM2, but according to two Australian studies, it might be anywhere between 2.9% and 8.7% annually. Independent of their weight, gestational diabetes is more likely to occur in PCOS women. Obesity does, however, appear to aggravate GDM development in PCOS. PCOS is regarded by the International Diabetes Federation as an inevitable risk factor for type 2 diabetes. (Nandi, Chen, Patel, & Poretsky)

A collection of cardiovascular risk factors known as the "insulin resistance syndrome" or metabolic "syndrome X" is usually connected to hyperinsulinemia or insulin resistance. (Haeffner , ve diğerleri, 1992, s. 41:715–22.). The metabolic syndrome is defined as abdominal obesity, blood pressure above 130/85 mm Hg, serum triglycerides above 150 mg/dL, serum HDL cholesterol under 50 mg/dL, and serum fasting blood sugar above 110 mg/dl. (Health., 2001, s. 01–3670). Patients who have metabolic syndrome are significantly more likely to develop coronary artery disease and die from any cause than healthy individuals without baseline diabetes, cardiovascular disease, or other chronic diseases. (Hu, ve diğerleri, 2004, s. 164:1066–76.)

Metabolic syndrome criteria are shown in **Table 1**.

Table 1. Metabolic syndrome criteria

Body Weight	≥88 cm for females
Lipid	TG 150 mg/dL or on prescribed TG Women's HDL-C 50 mg/dL or on HDL-C prescription
Blood pressure	≥ 85 mm Hg diastolic, ≥ 130 mm Hg systolic, or on a prescription for hypertension
Glucose	≥100 mg/dL (includes diabetes)
Insulin resistance	No more than three of the following five characteristics. (Grundy, 2008)

Elevated BMI and waist measurements may mask an excessive nutritional consumption, which is probably the true cause of metabolic syndrome. (Grundy, 2008)

Metabolic syndrome risk factors:

- Non-white race
- Sedentary life
- BMI> 25
- Age>40
- Cardiovascular system disease
- Hypertension
- PCOS
- Hyperandrogenemia
- Insulin resistance
- HAIR-AN
- Nonalcoholic steatohepatitis
- Impaired glucose tolerance, tip 2 DM

Treatment of PCOS's metabolic syndrome:

The primary line of treatment for PCOS's metabolic syndrome is lifestyle change through exercise and weight loss. Exercise on a regular basis lowers insulin resistance, lowers blood pressure, raises HDL cholesterol, and lowers VLDL levels. (Zimmerman , Kaufmann , & Fainaru). Visceral adipose tissue is reduced with weight loss, which enhances insulin sensitivity and blood pressure management. (Sowers, 2003). Pharmacologic therapy should be taken into consideration if ineffective. Although debatable, we think that insulin-sensitizing drugs are currently the drug of choice for controlling PCOS and concurrent metabolic syndrome in women. The most thorough evaluation of these medications in PCOS has been conducted on metformin. By increasing insulin peripheral glucose absorption and utilization in muscle tissue and reducing hepatic glucose synthesis, metformin increases insulin sensitivity. Metformin also lowers androgen levels in the blood and helps PCOS patients resume ovulation. (Moghetti, Castello , & Negri , 2000). Although studies on women are increasingly being undertaken, the majority of research on the benefits of decreasing CVD risk factors was initially conducted on men. Blood pressure reduction significantly lowers the risk of CVD in women (SHEP Cooperative Research Group (1991) Prevention, 1991). The pharmaceutical management of female hyperlipidemia is advantageous for both primary (Downs, 1998). Interventions for the metabolic syndrome may also be necessary for women with PCOS, a history of GDM, or preeclampsia.

Additionally, women of reproductive age must be treated with extra caution when prescribed medications to treat the symptoms of the

metabolic syndrome. The use of angiotensin-converting enzyme drugs during pregnancy has been related to an increased risk of birth defects and neonatal renal failure.. (Cooper, 2006). In women with PCOS, combined oral contraceptives can help with acne and hirsutism as well as menstrual cycle control. (De Leo, Caruso, & Scolaro, 2009)Some writers have turned their focus to the fundamental traits of the patients: obese, hyperandrogenic, insulin-resistant women are more likely than slim, less hirsute women to have a decline in metabolic profile in response to OCs. (Morgante, Massaro, Di Sabatino, Cappelli, & De Leo, 2018). An extensive spectrum of symptoms associated with androgen overproduction and ovulatory failure characterize PCOS, a complex condition. Metabolic dysfunction is more likely to occur in PCOS women, which necessitates routine monitoring for diabetes and CVD risk. While the majority of treatment is focused on alleviating the immediate symptoms, long-term health will benefit from dietary changes to alleviate metabolic abnormalities. Young women with PCOS frequently seek medical attention for irregular periods or infertility; at this point, it is possible to inform them of the increased long-term risk of metabolic issues associated with the syndrome so that they can make prompt and necessary lifestyle changes. (Yvonne & Reeves, 2017)

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CHAPTER XIX

PCOS AND CANCER

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by oligomenorrhea, hyperandrogenism and polycystic ovaries (1, 2). PCOS was first described by Stein and Leventhal in 1935 as hirsutism, amenorrhea, anovulation, infertility, and cystic ovaries (3, 4). PCOS is diagnosed by clinical, biochemical and via ultrasound (4). More than 25 follicle cysts are observed in PCOS and constitute approximately 10 ml of the ovarian volume (2). PCOS is the most common endocrine disorder in reproductive age patients in developed countries and is seen in 6-20% of reproductive age patients (5). Although the exact pathophysiology of PCOS is unknown, it is affected by both genetic and environmental factors (6, 7).

PCOS is associated with longer menstrual cycles, lower sex hormone-binding globulin levels, and higher androgen levels. This indicates hyperandrogenism in PCOS cases (1, 4, 8, 9). Some characteristic features such as hyperinsulinism seen in PCOS cases cause insulin resistance, hyperandrogenism and excessive LH secretion. Hyperandrogenism and oversecretion of LH cause overexpression of androgen receptors in the endometrium in cases of PCOS and overexpression of endometrial LH receptors in anovulatory PCOS, which has become the main cause of endometrial hyperplasia or carcinoma (1, 10-12). In addition, endometrial hyperplasia is an oncological risk factor for cases affected by PCOS (13). The risk of cancer among cases affected by PCOS has been a matter of debate over the years (14).

Oncological risk in PCOS cases can be induced by factors such as aging, lifestyle, sexual and reproductive health, higher or lower body mass index (BMI), diet and metabolism, and toxic habits (2, 9). There is evidence that these factors may contribute to oncogenesis and cancer progression in PCOS (15, 16) . Moreover, it was shown that the effect of sympathetic hyperactivity will cause norepinephrine secretion,

where increased norepinephrine acts as a biochemical switch for tumor angiogenesis (15, 17-19). In addition, several PCOS-associated genes were identified that show significant genomic changes in endometrial, ovarian, and breast cancers based on genomic analysis (20). Among these identified genes, the tumor suppressor gene PTEN has shown the highest number of mutations in endometrial cancer (20). However, DNA hypomethylation was detected in PCOS and irregular menstruation cases (20). In addition, the PI3K/Akt/mTOR signaling pathway is overactive in PCOS and ovarian cancer and endometrium. Activation of this signaling pathway is associated with the pathogenesis of PCOS and ovarian cancer (21, 22). However, point mutations in BRCA genes and MLH1 genes have been shown to increase the risk of ovarian cancer in PCOS cases with irregular menses (23).

Cancers related to chronic hormone stimulation in women include endometrial, ovarian, and breast cancer. In cases with PCOS, chronic estrogen stimulation can often cause endometrial hyperplasia or endometrial cancer (9, 24-27). Progesterone resistance is also a trait shared by some PCOS patients and may increase oncogenic risk in PCOS cases with deregulation of endometrial gene expression (10). The primary reason of PCOS increases the risk of endometrial cancer is the prolonged exposure of the endometrium to unopposed estrogen, caused by anovulation (10). Other risk factors for endometrial cancer are obesity, long-term unopposed estrogen use, not giving birth, infertility, Diabetes Mellitus and Hypertension. Many of these factors also contribute to the development of PCOS (28). Therefore, cases diagnosed with PCOS were found to have a threefold increased risk of developing endometrial cancer due to prolonged exposure to excessive estrogen and unstable progesterone levels in the human endometrium (10, 12). This relationship was first published in 1949, 14 years after PCOS was first described by Freiler Stein and Michael Leventhal. It was also reported that anovulatory cases with PCOS with an

endometrial thickness > 7 mm or amenorrhea for more than 3 months were 8.7% more likely to develop endometrial hyperplasia (2, 10). According to studies, cases with PCOS may have a higher risk of developing endometrial cancer than those without PCOS (28). Studies also show that the risk of developing endometrial cancer from PCOS is 2.7-3 times (4, 9, 10, 12, 29). Ding et al (12) showed in their study that PCOS is associated with endometrial cancer (1, 12, 30, 31). Contrary to studies, the Danish study did not find a higher prevalence of endometrial cancer in cases with PCOS or hyperandrogenism than in controls (32-34).

Although the direct relationship of PCOS with breast cancer and ovarian cancer has not yet been established, the incidence of these cancers in PCOS patients has been observed in various studies over the years (1, 35, 36). The growth of breast and ovarian carcinoma from hormone-sensitive tumors can be explained by the sustained increase in serum estrogen concentrations (31).

Ovarian cancer and PCOS are strongly related; however, the underlying molecular mechanism is largely unknown (37). Hyperandrogenism is an important component of PCOS. Risch suggested in 1998 that factors that contribute to androgen stimulation of ovarian cells may be linked to ovarian cancer. Animal studies have shown that testosterone increases the proliferation of epithelial cells in the ovary. Androgen receptors are abundant in serous borderline tumors. This suggests that androgens may be a factor in the progression of ovarian cancer (1, 38). Studies have shown that androgens are associated with the pathogenesis of ovarian cancer in PCOS patients (39-41). In one study, cases with PCOS were found to be twice as likely to develop ovarian cancer as those without PCOS (31, 42). In contrast to these studies, no association of PCOS with ovarian cancer was found in the study of Ding et al. and in a population-based cohort study in Taiwan in 2018 and other studies (1, 12, 43). In addition, they reported that the risk of

ovarian cancer was not very high in cases with PCOS (30). However, Gottschau et al. also found an insignificant risk of ovarian cancer in cases with PCOS when compared with the general population (9). According to a population-based cohort study of Lundberg et al., the risk of ovarian cancer was found to be higher in infertile cases (44). Despite the lack of studies on the risk of ovarian cancer in PCOS patients, studies suggest that tissues in the ovaries of irregular menses show DNA hypomethylation and miRNAs are comparable to ovarian cancer, suggesting that PCOS patients are at increased risk for ovarian cancer (2, 10).

Breast cancer is a heterogeneous cancer. The incidence, clinical features, and prognosis of breast cancer vary markedly by ethnicity and race (45). The relationship of breast cancer to PCOS is not clear, but studies are ongoing to find a strong association between them. Data obtained from various institutions have shown that breast cancer is the most common cancer in the cases (46). Increased androgen level is positively associated with the development of both PCOS and breast cancer (7). Contrary to the study, although the effects of androgen on breast cancer development in PCOS are not fully understood, studies have shown evidence of the role of estrogen in breast cancer development (47-49) While there are studies reporting a link between PCOS and breast cancer, there are studies showing that it is not (27, 43, 44, 50, 51). In the long-term follow-up of 786 cases diagnosed with PCOS, breast cancer was found to be the most common cause of death (52).

There are not enough studies to understand whether there is a relationship between PCOS and cancers of the vagina, vulva and cervix. Furthermore, there does not appear to be any plausible mechanism to explain the correlation between PCOS and these cancers (31). In a cohort study by Gottschau et al., an increased risk of colon, kidney, and brain cancers was reported among PCOS cases, but the risk

of other types of cancer, such as lung cancer, melanoma, and other types of skin cancer, was not significant (9).

One of the key drugs used in PCOS management is oral contraceptives. Studies have shown that oral contraceptives interfere with cancer-related regulation and reduce the risk of developing cancer in cases with PCOS (12, 53).

In the current study of Rubiat et al., PCOS cases were found to be more susceptible to developing endometrial cancer than other reproductive cancers, however, there was conflicting evidence linking PCOS to ovarian or breast cancer. No strong correlation was found between PCOS and non-reproductive cancers. Impaired hormonal balance, hyperinsulinemia, high estrogen level, chronic inflammation, sympathetic hyperactivity, hyperandrogenism, and low progesterone level have all been found to be associated with PCOS progression and have also been shown to contribute to oncogenesis and cancer progression in PCOS. Based on PCOS-related genes, it was found to show significant genomic changes in endometrial cancer, ovarian cancer and breast cancer (54).

In conclusion, there is an increased risk of endometrial cancer in cases with PCOS. The risk of breast cancer and ovarian cancer in cases with PCOS is not significantly higher than in cases without PCOS. It has been reported that the risk of ovarian cancer is reduced in cases with PCOS, but most of this decrease was found in the endometrioid histological type. The relationship between PCOS and gynecological cancers is complex. Future prospective cohort studies evaluating the relationship between PCOS and endometrial, ovarian and breast cancer are required. Thus, it will both enable the evaluation of cancer-related factors in PCOS cases and guide the cases to an individualized treatment approach (55).

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CHAPTER XX

DIET & EXERCISE IN POLYCYSTIC OVARY SYNDROME

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Introduction

Polycystic ovary syndrome (PCOS) is an endocrinological and gynecological disorder affecting women in the reproductive period characterized by hyperandrogenism and chronic anovulation, with multiple environmental and genetic factors in its etiology. PCOS has short-term risks of infertility, hirsutism, alopecia, cycle disorders and pregnancy loss, and long-term risks of cardiovascular disease, type II diabetes mellitus, psychosocial problems and endometrial cancer. In addition, problems such as anxiety, decreased sexual desire, suicide attempts and eating disorders are more common in women with PCOS (Hotun Şahin & Demirgöz Bal, 2015; Kılıç, Güler & Alataş, 2020).

The International Evidence-Based Guidelines for the Evaluation and Management of PCOS emphasized the importance of diet in PCOS and recommended body weight management and exercise interventions as first-line treatment for women with PCOS who are mostly overweight and obese (Kasım Karakaş et al., 2004). Body weight management is defined as preventing excessive body weight gain or achieving and maintaining a low body weight in women who are already overweight. It is best achieved through multidisciplinary lifestyle management including diet, exercise and behavioral therapy. Lifestyle management improves the reproductive, metabolic and psychological features of PCOS (Çağıran, 2011).

This chapter aims to emphasize the effect of nutrition and exercise therapy on symptoms in polycystic ovary syndrome.

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome is a common endocrine disorder that can vary depending on the diagnostic criteria and population; it can be seen in 6-10% of women of reproductive age according to the US National Institutes of Health (NIH) criteria and 15% when the Rotterdam criteria (ESHRE/ASRM) are applied (Toptaş & Aksu, 2021).

Polycystic ovary syndrome is characterized by an increase in the fat layer, obesity and excessive stimulation of insulin. These events cause gonadotropins to be stimulated, leading to disruption of hormone balance. Disruption of hormonal balance leads to an increase in the tendency of individuals to gain weight. Although hyperinsulinemia and insulin resistance are seen in individuals with PCOS with or without obesity, obesity alone is the cause of insülin resistance. Therefore, the risks are higher in obese individuals with PCOS (Aşçı & Kocaöz, 2019; Smith & Taylor, 2011).

Individuals with polycystic ovary syndrome present to the hospital with multiple symptoms, mostly in the peripubertal period. PCOS has many symptoms such as acne, hirsutism, alopecia, clitoral hypertrophy, ovulation disorder, voice thickening, metabolic syndrome, insulin resistance, depression and eating disorders (Aşçı & Kocaöz, 2019; Hotun Şahin & Demirgöz Bal, 2015).

Polycystic ovary syndrome and diet

The basis of leading a healthy life is healthy nutrition. Optimal nutrition not only protects individuals against malnutrition by providing sufficient nutrients for individuals to continue their lives, but also

protects individuals against chronic diseases that may occur due to nutrition (Serintürk, 2008).

Nutritional therapy is one of the most important treatments that should be applied with drug therapy in PCOS. Because weight loss is more difficult in individuals with PCOS due to insulin resistance. One out of every two individuals with PCOS has obesity (Toptaş & Aksu, 2021). According to studies, it is recommended that only nutritional therapy should be applied primarily in PCOS, and drug therapy should be added in cases where there is no adequate response (Khort et al., 1993). It is known that in cases where only drug therapy is applied, there is improvement in the acute period of the disease, but the picture becomes more complicated in the long term. Although the clinical usefulness of body weight loss in polycystic ovary syndrome has been emphasized, there is no clear consensus on the content of nutritional therapy. In PCOS, adipose tissue increases with the increase in body weight and hormone imbalances occur (Serintürk, 2008). There is a strong relationship between obesity and impaired glucose tolerance, menstrual cycle disorders, hyperandrogenism and infertility in individuals with PCOS (Çağıran, 2011).

Even moderate weight loss has been found to be effective in correcting metabolic disorders associated with PCOS. Therefore, nutritional therapy aims to control weight, improve plasma lipids, stabilize blood glucose, normalize androgen levels, reduce the number of ovarian cysts and decrease insulin resistance (Şanlı Ak, 2017). It is stated that only 5% weight loss is effective in regulating the menstrual cycle with a decrease in androgens and insulin resistance (Günalp & Tuncer, 2004).

It is stated that weight loss of 2-5% in obese individuals with PCOS and anovulation is effective in the onset of ovulation and increased insulin sensitivity, as well as decreased insulin resistance due to decreased abdominal adipose tissue (Aşçı & Kocaöz, 2019; Uludağ et al., 2013).

In the general population, general recommendations for body weight management in relation to the dietary components of lifestyle interventions include a low fat (about 30% of energy, about 10% saturated fat, <300 mg cholesterol daily), moderate protein (about 15%), high carbohydrate (about 55%) and high fiber diet, and moderate regular exercise (Krauss et al., 2000). However, the specific diet composition that should be included in a lifestyle management program is controversial. In the general population, research evaluating the effects of varying dietary composition or glycemic load (GL) on body weight loss or maintenance and changes in metabolic outcomes is conflicting. From studies evaluating a range of dietary compositions, such as changing the amount or type of dietary protein, fat or carbohydrate, including high-protein, low-glycemic index (GI), very low-carbohydrate or diets that alter the fatty acid profile, no clear optimal dietary composition has been identified (Larsen et al., 2010; Gençal, 2022). However, even a 5% dietary weight loss is very important for the improvement of PCOS symptoms (Aşçı & Kocaöz, 2019; Faghfoori et al., 2017).

Carbohydrates

In the human body, 55-60% of energy is provided by carbohydrates, which are macronutrients. In PCOS, where weight loss is the primary treatment modality, the amount and type of carbohydrate intake with diet is important. Because carbohydrates affect insulin response and postprandial blood glucose level (Isharwal et al., 2009). The basis of nutritional therapy in PCOS is to reduce simple carbohydrates and meet 40% of energy from complex carbohydrates (Şanlı Ak, 2017; Serintürk, 2008). Foods with simple carbohydrates (refined foods) and high saturated fat content promote inflammation in women with PCOS and stimulate androgen production in the ovary, independent of excessive adiposity and insulin resistance (Barrea et al., 2018). Consumption of a diet rich in complex carbohydrates has been associated with greater insulin sensitivity. It has been suggested that insulin sensitivity may be a key factor in regulating ovulatory function and fertility (Calcaterra et al., 2021).

Since the composition of nutritional therapy may vary according to the dietary assessment, habits and metabolic goals of individuals, there is no clear recommended carbohydrate amount for women with PCOS (Papavasiliou & Papakonstantinou, 2017). However, based on studies, it has been reported that 45-50 percent of daily energy should be met from carbohydrates with low GI in the nutritional treatment of women with PCOS (Lydic & Juturu, 2008). Consumption of high GI and sugary foods that trigger more hunger should be reduced because consuming foods with low GI provides satiety and creates a feeling of fullness (Papavasiliou & Papakonstantinou, 2017). In a study

comparing obese and PCOS patients who lost weight with traditional healthy diet and low GI, it was determined that menstrual irregularities of women who lost weight with low GI improved (Marsh et al., 2010).

Studies have been conducted on the effects of high protein, low carbohydrate and low protein, high carbohydrate diets on PCOS (Stamets et al., 2004; Layman et al., 2003). In these studies, it was reported that there was no significant difference in body weight loss in terms of different protein content of diets. No significant differences were also observed in fasting insulin levels or HOMA values between low-carbohydrate and high-carbohydrate diets. However, a lower postprandial insulin response was reported in subjects consuming a low-carbohydrate diet (Farnsworth et al., 2003; Layman et al., 2003). In a recent study, it was reported that both fasting and postprandial insulin levels were reduced by a low-carbohydrate diet (Gençal, 2022).

Proteins

Protein diets play an important role in weight loss and diabetes management in individuals with polycystic ovary syndrome. Proteins should provide 15-20% of energy intake from nutrients. However, there is not enough data in the literature about the positive effect of high-protein dietary management on insulin resistance (Çağıran, 2011).

Chronic low-grade inflammation plays a role in the pathogenesis of polycystic ovary syndrome. Recently, it has been suggested that dietary protein source plays an important role in the modulation of immunity and low-grade inflammation. However, some studies have reported that plant protein-dominated diets have anti-inflammatory and animal

protein-dominated diets have pro-inflammatory effects (Markova et al., 2020; Hruby & Jacques, 2019; Richter et al., 2015).

Since proteins are digested slowly, their effect on blood glucose is relatively low. One study reported that a high-protein diet for six weeks led to improvements in both fasting and postprandial glucose levels (Skytte et al., 2019). Daily high protein intake improves reproductive and endocrine functions (Mehrabani et al., 2012). In a study conducted on individuals with PCOS, a standard (15% protein) and a high-protein (40%) diet was administered to one group and the other group, respectively, for six months. It was found that the high-protein diet group lost more fat and weight than the other group, as well as decreased blood glucose levels and waist circumference (Sorensen et al., 2012). In a study conducted by Palomba et al. (2007) on PCOS and obese individuals, it was found that low energy high protein diet and exercise for 24 weeks had positive effects on fertility and menstrual cycle, and insulin levels and sex hormones were significantly improved. However, in another study conducted on individuals with PCOS, it was found that a high-protein diet was not more effective on reproduction and metabolic abnormalities than a high-carbohydrate diet (Moran et al., 2004). Moran et al. (2003) conducted a study on obese individuals with polycystic ovary syndrome and found that weight loss was 7-5%, free testosterone, fasting insulin, lipid and LDL levels decreased and sex hormone binding globulin (SHBG) levels increased in individuals who were on a high protein (30%) and 1434 kcal/day diet for 12 weeks.

In the literature, the positive effects of high protein intake in individuals with PCOS are mentioned, but there is no general consensus on the definition of a high protein diet. High-protein diets aim for 30% protein intake for weight loss. There are data that high-protein diets provide body weight loss in a short time compared to other diets (Şanlı Ak, 2017).

As a result, it was found that diets high in protein and low in carbohydrate were associated with more fat and less lean mass loss. It has been reported that individuals who follow diets containing moderate carbohydrate and high protein can maintain their diets for up to one year (Westerterp, 2009). Although the positive effects of high-protein diets on individuals with PCOS have been observed, there is no consensus in the literature about the optimal diet composition for PCOS (Şanlı Ak, 2017).

Fats

It is recommended that 25-30% of total energy in the diet should consist of fats and 10% of these fats should be low saturated fats. In the literature, some types of carbohydrates and fats are reported to increase insulin resistance. It has been reported that excessive consumption of saturated fatty acids increases insulin resistance, while a diet rich in unsaturated fatty acids decreases insulin resistance (Çağıran, 2011). However, favorable effects of fat quality on insulin sensitivity have been observed in individuals receiving <37% of their total energy intake as fat. The long-chain PUFAs found in fish oil, eicosapentaenoic acid and docosahexaenoic acid, have beneficial effects on metabolic parameters in patients with diabetes, but specific evidence for PCOS is

not available at this stage. Although the Mediterranean diet, rich in monounsaturated fatty acids (MUFA), is widely accepted as the gold standard for healthy diets, its potential benefits in patients with PCOS have not been documented (Gençal, 2022).

Polyunsaturated fatty acids (PUFAs) help to prevent uncontrolled insulin release by reducing insulin resistance, thus reducing androgen release. Kalgaonkar et al. (2011) found that a diet rich in unsaturated fatty acids had a significant effect on lipid and androgen levels in individuals with PCOS (Kalgaonkar et al., 2011). It is recommended that individuals with PCOS take omega-3 fatty acids rich in FFA. Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been associated with a favorable effect on insulin resistance. Supplementation with omega-3 fatty acids, α-lipoic acid and N-acetylcysteine has been reported to exert anti-inflammatory and antioxidant effects and lead to improvements in insulin sensitivity in women with polycystic ovary syndrome (Calcaterra et al., 2021). Although the use of omega-3-rich fish oil does not cause a difference in endogenous glucose production and utilization, it causes an increase in glycogen storage (100%) and fat oxidation (35%) and a decrease in carbohydrate oxidation (35%). In addition, fish oil decreases the insulinemic response after oral fructose intake and inhibits lipogenesis with the contribution of liver enzymes (Kasim-Karakas et al., 2004). In a study on individuals with PCOS in which the effects of omega-3 fatty acids (4 g daily) on blood pressure, blood lipids and cardiometabolic risk factors were examined, it was determined that triglycerides, systolic and diastolic blood pressure

decreased significantly (Cussons et al., 2010). Good et al. (2006) examined the effects of the FWW diet and found that the diet caused significant weight loss but did not cause any change in waist circumference (Good et al., 2006).

Fiber foods

A diet consisting of lean protein sources, unsaturated fat and high fiber is important in individuals with polycystic ovary syndrome (Krystock, 2014). Dietary fiber has a hormone metabolism-regulating effect as it reduces insulin secretion by slowing the rate of glucose absorption after a meal. It also increases feelings of satiety, potentially reducing calorie intake and helping with body weight management (Cutler, Pride & Cheung, 2019). Fibers also contribute to the removal of toxic substances from the body. In the absence of adequate fiber intake, there are imbalances in blood glucose levels and weight gain, hypercholesterolemia, and increased testosterone and estrogen levels. Diets with high fiber content play a protective role in the pathogenesis of metabolic diseases. In addition to the positive effects of dietary fiber on metabolic parameters in PCOS, another point to consider is its capacity to act as a prebiotic on the gut microbiota. Increased intestinal permeability, increased endotoxemia due to LPS activates the immune system and inflammation and increases hyperandrogenism and insulin resistance (Cutillas-Tolín et al., 2021). In a review, it was reported that fiber intake was positively correlated with serum SHBG levels and that modern diets with low fiber and high refined carbohydrates cause insulin resistance and obesity (Kamran et al., 2017). The amount of dietary fiber specific for women with PCOS is not specified in the

literature, but a dietary fiber intake of 25-32 grams per day is recommended for adult women (Barber et al., 2020). Plant phytoestrogens found in foods such as oats, barley, tofu, beans, rice, rice bran, lentils, sesame, soybeans, wheat germ, flaxseed, cherries, carrots, strawberries and apples bind excess estrogen in the body, reducing its effect and showing a weaker estrogenic effect. In addition, phytoestrogens stimulate SHBG production and cause a decrease in hormone levels in the blood (Serintürk, 2008).

Vitamins

Some drugs used in the treatment of polycystic ovary syndrome reduce the absorption of many vitamins. Drugs used in the treatment of PCOS can lead to decreased absorption of vitamin B12 (10-30%). Drugs containing estrogen, progesterone and synthetic progestins cause malabsorption of vitamin B6, B12, vitamin C, niacin, riboflavin, zinc, magnesium, selenium and folic acid. Biguanide group (metformin) drugs cause megaloblastic anemia and malabsorption of vitamin B12, coenzyme and folic acid (Çağıran, 2011). It is known that vitamin B12 (cobalamin) levels decrease during metformin treatment. Vitamin B12 is strongly associated with serum homocysteine. Homocysteine levels may increase in women with PCOS due to decreased vitamin B12 levels during metformin treatment. Elevated homocysteine is associated with an increased risk of atherosclerotic and thromboembolic disorders as well as hyperinsulinemia. It has been suggested that folate and B12 supplementation may be promising for reducing homocysteine levels (Calcaterra et al., 2021; Meng et al., 2016). Vitamin supplements are preferred to act on various pathophysiological pathways in PCOS and

to improve hormonal and metabolic profiles. There is evidence reporting positive effects of vitamin supplements on immature oocytes, hyperandrogenism, insulin resistance and oxidative stress in women with polycystic ovary syndrome (Iervolino et al., 2021; Garg, Malhotra & Rawat, 2020; Jamilian & Asemi, 2015).

Magnesium is known to have important roles in insulin and glucose hemostasis. Intracellular magnesium acts as a cofactor for multiple enzymes in carbohydrate metabolism. In a study conducted on individuals with PCOS, high dose magnesium intake was found to reduce the risk of type 2 diabetes mellitus and metabolic syndrome (Zemel, 2004). Although there is a significant relationship between type 2 diabetes mellitus and magnesium intake in the literature, the number of studies on this subject is limited (Şanlı Ak, 2017).

A study on women with PCOS reported a decrease in insulin resistance and an increase in insulin sensitivity in the group receiving 60,000 IU/week vitamin D supplementation for twelve weeks compared to the control group. These findings suggest an underlying role for vitamin D in glucose homeostasis. A review reported that high doses of vitamin D supplementation (≥4000 IU/day) for at least twelve weeks may improve glucose levels, insulin sensitivity, hyperlipidemia and hormonal functioning in women with PCOS (Menichini & Facchinetti, 2020). Wehr, Pieber, and Obermayer-Pietsch (2011) reported that 20,000 IU/week of vitamin D supplementation for twenty-four weeks improved the menstrual cycles of women with PCOS (Wehr et al., 2011). According to the results of the research on whether vitamin D supplementation will reduce insulin resistance and glucose levels in

individuals with PCOS; it was determined that 50,000 IU vitamin D supplementation did not have the expected effect on insulin resistance and sensitivity (Alkharfy et al., 2013).

Recommendations regarding nutrition to ensure glucose control in individuals with PCOS are as follows;

- Three main meals and 2-3 snacks should be organized and meals should not be skipped.
- The ratio of carbohydrate and protein in meals should be balanced as 2/1.
- Avoid products with a high glycemic index such as sugar/sugary products, refined carbohydrates (pasta, rice, white bread, etc.), starchy products (potatoes), grapes, bananas and salvaged fruits.
- Alcoholic drinks with high carbohydrate content, such as beer, should be avoided.
- It is important to consume foods with a low glycemic index and high fiber content such as fruits, vegetables, legumes, whole grain products and peas.
- Stimulants such as cigarettes, coffee and tea should be avoided.
- Stress triggers the hormone cortisol, causing blood glucose levels to rise and insulin resistance to increase. Therefore, allergic foods that may cause stress in the organism and cause glucose irregularity should be avoided.

Polystic ovary syndrome and exercise

Exercise is one of the most important building blocks after diet in the treatment of PCOS. However, there is no clear study on the type, duration and intensity of exercise in the literature. However, exercise supports general health, weight loss and insulin sensitivity (Harrison et al., 2011). High BMI may trigger infertility by causing anovulation. In addition to infertility, it can cause pregnancy complications and pregnancy losses in the second and third trimesters (Aşçı & Kocaöz, 2019). Regular exercise reduces insulin requirements and decreases HbA1C levels (Church et al., 2010). Moderate to high intensity aerobic physical exercise improved metabolic and reproductive outcomes in women with PCOS and reduced indices related to chronic anovulation, cardiometabolic risk, insulin resistance and obesity (Ribeiro et al., 2021). Exercise reduces BMI, waist circumference, visceral adipose tissue and increases weight loss (Hamdy et al., 2001). Since visceral adipose tissue is lighter than subcutaneous fat, it is associated with insulin resistance. In the literature, it is stated that regular exercise in individuals with PCOS contributes to improvement in lipid profile, hirsutism, menstrual cycle and ovulation, as it reduces waist circumference and improves insulin sensitivity (Mehta & Varma 2019; Tiwari, Pasrija & Jain 2019).

Regular exercise reduces stress. Physical activities such as walking/jogging, sports activities (sports branches or classes), gardening should be performed for at least 30 minutes a day (Crete & Adamshick, 2011; Glintborg et al., 2012). At least 150 minutes of exercise per week is recommended for individuals with PCOS and

overweight/obese (BMI ≥25kg/m2) (Erdönmez et al., 2011). It is known that performing cardio exercises with high intensity (60%-90% maximum heart rate) for 90 minutes weekly reduces the clinical symptoms of PCOS (Şanlı Ak, 2017).

According to studies, progressive aerobic exercise for 16 weeks was found to reduce BMI, waist circumference, total cholesterol level, systolic and diastolic blood pressure. Progressive aerobic exercise was found to improve the cardiometabolic and cardiorespiratory profile of women (Costa et al., 2018; Ramos et al., 2016). Studies emphasize the importance of supervised exercise training as a therapeutic approach for individuals with PCOS. In addition, it is stated in the literature that exercise has positive effects on depression and sexual functions in individuals with PCOS (Kogure et al., 2020; Lopes et al., 2018).

In a 20-week study examining the effects of regular exercise and diet, 94 individuals with PCOS and obesity were divided into two groups. One group received only diet and the other group received a combination of diet and exercise. As a result of the study, it was determined that the group exercising with diet lost more adipose tissue and less muscle tissue compared to the other group (Giallauria et al., 2009).

In a study investigating aerobic (treadmill) exercise for 45 minutes daily for 12 weeks in individuals with PCOS, it was found that exercise contributed to improvement in hormone levels (Kirthika et al., 2019). In another study, it was determined that continuous or intermittent exercise contributed to improving the perception of general and mental health as well as social, physical and emotional functionality of

individuals with PCOS. In addition, it was determined that continuous or intermittent aerobic exercise practices were equally effective in reducing hyperandrogenism and anthropometric indices and improving quality of life in individuals with PCOS. For all these reasons, exercise protocols should be included in the clinical setting to improve the social, mental, physical health and clinical parameters of individuals with PCOS (Riberio et al., 2016).

In the literature, it is reported that menstrual cycle disorders and fasting insulin levels increase in women who sleep less than 6 hours. It has been reported that regular exercise contributes to sleep patterns and that insulin levels and menstrual cycles improve with sleep patterns (Lim et al., 2016; Tiwari et al., 2019).

The type, duration, frequency and intensity of physical activity should be questioned when taking the anamnesis of individuals with PCOS. Vigorous aerobic activity for 30 minutes or longer at least 3 days a week is recommended. It is stated that exercise on certain days of the week/intermittent strength training/resistance training benefits androgen levels (Shele, Genkil & Speelman 2020). The International Evidence-Based Guidelines for the assessment and management of PCOS (2018) recommend at least 150 minutes/week of moderate-intensity physical activity or 75 minutes/week of vigorous-intensity activity, including muscle-strengthening activities, on two intermittent days of the week in adults aged 18-64 years.

Conclusion and recommendations

It is known that exercise and a balanced diet have positive effects on PCOS symptoms in individuals with polycystic ovary syndrome. In addition to improvement in PCOS symptoms, exercise and nutrition have been found to reduce adipose tissue and waist/hip ratio. In addition, it was found that nutrition and exercise therapy applied to individuals with PCOS reduced the risk of cardiovascular disease, diabetes mellitus and gestational diabetes mellitus, and improved lipid metabolism, menstrual cycle disorders and ovulation. In addition, nutrition and exercise have been found to reduce the symptoms of hormonal disorders such as acne, hirsutism and hyperandrogenism. Exercise and balanced nutrition reduce the rates of fetal loss and complications that may occur in advanced gestational weeks and increase pregnancy rates. It is important for women with PCOS to exercise in parallel with a balanced diet. In conclusion, it is very important to establish and maintain a lifestyle change in order to prevent the symptoms and risks associated with PCOS.

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CHAPTER XXI

PHARMACOLOGICAL TREATMENTS IN PCOS

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THE THERAPIES THAT ARE CURRENTLY ADVISED FOR PATIENTS WITH PCOS

The treatment of PCOS nowadays is based on the patient's symptoms, and it also depends on whether or not fertility therapy is being attempted.

To treat menstrual irregularities and the physical manifestations of hyperandrogenism (hirsutism, acne, and androgen-related alopecia), combined oral contraceptive pills (OCs) comprised of estrogens and progestins are commonly prescribed to women with PCOS who are not seeking assistance with fertility. These women do not want to have children and are not interested in fertility treatment (Teede et al., 2018). Many of the effects of OCs are anti-androgenic. Reduced gonadotrophin release from the pituitary and subsequent androgen production from the ovaries leads to lower testosterone levels and bioavailability. Additional anti-androgen drugs may be utilized in cases when cosmetic treatments and OCs are insufficient to control hyperandrogenism. These drugs, like spironolactone and finasteride, interfere with the androgen production process or inhibit the androgen receptor (AR). Metabolic symptoms of PCOS may be treated with weight reduction and dietary strategies alone or in conjunction with oral insulin sensitizers (such as metformin) (Teede et al., 2018). The effects of OCs that are anti-androgenic are varied. Estrogens and progestins inhibit the release of gonadotrophin from the pituitary gland. This, in turn, decreases the synthesis of androgens downstream in the ovaries, which finally results in a lower amount of testosterone and its bioavailability. Additional anti-androgen drugs may be utilized as a

treatment option for hyperandrogenism in cases when cosmetic operations and OCs are not effective enough to control the condition. These either inhibit the androgen receptor (AR) or modify the route that androgens take during their manufacture (for example, spironolactone and finasteride). It is suggested to lose weight and make dietary changes either on their own or in conjunction with oral insulin sensitizers like metformin in order to treat the metabolic symptoms of PCOS (Teede et al., 2018). In order to cure infertility in women who have PCOS, an alternative method is required since OCs stop ovulation and anti-androgens are harmful to a developing male fetus. Women with PCOS who want to have children must use this method. Instead, strategies for weight reduction and medications that stimulate ovulation are often recommended. Ovulation may be pharmacologically induced using the drug letrozole, which is considered a first-line intervention. Letrozole inhibits the aromatase-induced conversion of androgens to estrogens, which results in an increase in the release of follicle-stimulating hormone (FSH). This, in turn, promotes follicular maturation by reducing the amount of negative feedback experienced by the body (Elizur & Tulandi, 2008). Clomiphene citrate, which is a selective estrogen receptor modulator, is also used for ovulation induction. This medication is often used with metformin, however, there is some concern that it may raise the risk of endometrial cancer (Brinton et al., 2013). Women who have PCOS and are receiving fertility therapy with letrozole or clomiphene citrate have an increased risk of ovarian hyperstimulation syndrome (OHSS). This is a significant side effect that affects the ovarian vasculature and, in rare circumstances, might necessitate hospitalization. Women who have

PCOS and are undergoing fertility treatment with letrozole or clomiphene citrate have an increased risk of ovarian hyperstimulation syndrome (OHSS).

INNOVATIVE AND CUTTING-EDGE THERAPY MODALITIES NOW AVAILABLE FOR PATIENTS WITH PCOS

Existing therapies for PCOS's endocrine, metabolic, and reproductive manifestations are helpful, but they may be enhanced. First, many existing medications have undesirable side effects, including weight gain with OC usage, gastrointestinal problems with metformin, and a higher risk for OHSS with fertility treatments. Second, there are situations in which hormone therapy is inappropriate, such as in people with breast cancer, venous thrombosis, or a history of stroke. Several innovative medications for PCOS control have shown promise in both animal research and preliminary human trials, which is encouraging.

INNOVATIVE THERAPIES AIMED TOWARD REDUCING EXCESS ANDROGENS

Hyperandrogenism is a key factor in the primary pathogenesis of PCOS, and it is the underlying cause of many of the distressing overt symptoms that PCOS patients experience. In line with this notion, the metabolic and reproductive characteristics of PCOS in animal models are often caused by prenatal or peripubertal exposure to excessive levels of androgens (Stener-Victorin et al., 2020). Therefore, therapeutic lowering of androgens, as well as AR inhibition, are both significant methods in the treatment of PCOS. It is possible that starting anti-androgen medication at an early stage is also essential for

improved reproductive results. Women diagnosed with PCOS who received anti-androgen medication at an earlier age (before the age of 18) were shown to have a higher fertility rate when compared to women who received treatment at a later age. The research was conducted using a retrospective population-based methodology in Sweden (Elenis, Desroziers, Persson, Sundström Poromaa, & Campbell, 2021). In addition, research conducted on mice suggests that an excessive amount of androgens may have long-term effects on the quality of follicles and oocytes, which may continue to impede fertility even after hyperandrogenism has been restored (Bertoldo et al., 2019).

Cross-reactivity between direct AR antagonists and GABA-A receptors in the brain raises the possibility of convulsive activity (Henderson, 2007). Peripherally selective second-generation AR antagonists having a limited potential to penetrate the blood brain barrier, and as a result, they might be a useful tool for the treatment of PCOS. This is because they are peripherally selective. In point of fact, a clinical investigation indicated that the treatment of hirsutism in women with PCOS with the peripherally selective AR antagonist bicalutamide (Casodex) in conjunction with OCs was more successful than therapy with OCs and placebo (Moretti et al., 2018). Although there are presently no clinical studies examining darolutamide as a therapy for PCOS, darolutamide (ODM-201, Nubeqa) is another AR antagonist with limited blood-brain barrier penetrance. Darolutamide has recently acquired permission in various countries for the treatment of specific prostate malignancies (Fizazi, Smith, & Tombal, 2018). The use of direct AR blockers is sadly not a practical option for individuals seeking reproductive therapy

because of the hazards to the foetus. Peripheral AR antagonists, on the other hand, may be effective for the treatment of PCOS symptoms in women that are connected to cosmetic hyperandrogenism. In addition, research conducted on animals suggests that the reproductive and metabolic problems that are characteristic of PCOS are caused by the effects of androgens in the brain, rather than in the body's periphery (Caldwell et al., 2017). Even while the ovaries are most likely to be the primary source of excess androgens in PCOS, adrenal androgens may also play a significant role. For instance, research has revealed that up to half of women who have PCOS have an abnormally high level of dehydroepiandrosterone sulphate (DHEAS), which is a measure of adrenal androgen synthesis (Goodarzi, Carmina, & Azziz, 2015). In addition, women who have congenital adrenal hyperplasia have many of the same symptoms as those who have PCOS, including an ovary that appears polycystic (Guarnotta et al., 2020). The stress response is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, which adrenal androgens play a role in. The stress response begins in the hypothalamus, where corticotropin-releasing hormone (CRH) promotes the production of adrenocorticotropic hormone (ACTH) from the pituitary gland, which in turn stimulates the release of cortisol and androgens from the adrenal glands. It is not known if hyperandrogenism in PCOS is caused by HPA hyperactivity or adrenal androgen production. A prenatally androgenized mouse model of polycystic ovary syndrome showed aberrant expression of Crh and Crhr1 in the hypothalamus (Manti et al., 2018). In addition, a recent research found that the level of hirsutism in teenagers with PCOS was connected with the amount of adrenal androgen production (Taylor et

al., 2022). It is interesting to note that one of the possible treatments for PCOS being researched right now is a modulator of CRH signalling. Tildacerfont is a CRHR1 antagonist that is nonsteroidal and may be taken orally. It works by inhibiting pituitary ACTH, which in turn limits the synthesis of adrenal androgens. In women who have PCOS and have high levels of adrenal androgens, a phase 2 clinical research that is presently enrolling participants is looking at the effectiveness and safety of tildacerfont.

Reducing androgen bioavailability is an alternative strategy for treating androgen excess. Directly modulating the clearance and bioavailability of sex steroids in the blood and target tissues, sex hormone-binding globulin (SHBG) is a sex hormone transporter with high affinity for testosterone. More and more research points to SHBG as a potentially diagnostic biomarker and treatment target for polycystic ovary syndrome. PCOS is linked to low SHBG levels (Deswal, Yadav, & Dang, 2018). Moreover, new genetic association studies suggest that there may be a relationship between the two (C. Wang et al., 2022; Zhang, Movva, Williams, & Lee, 2021). A recent research indicated that women with greater SHBG had a lower prevalence of PCOS comorbidities. This finding is interesting because it shows that therapeutically boosting SBHG levels in women with PCOS might have a protective impact (Ruth et al., 2020).

TARGETING NEUROENDOCRINE DYSFUNCTION FROM A CLINICAL PERSPECTIVE

In regulated ovarian stimulation, GnRH antagonists are used for direct manipulation of GnRH to reduce GnRH-mediated release of LH and

FSH in fertility therapies. However, GnRH antagonists generally cause an increase in the quantity but a reduction in the quality of oocytes, which increases the risk of OSS in women with PCOS (Lambalk et al., 2017). Aside from its use in the treatment of infertility, there is little clinical data to suggest that GnRH antagonists would be of any assistance to the treatment of PCOS. However, preliminary findings from an experiment using a mouse model of PCOS that was produced by prenatal exposure to anti-Mullerian hormone indicate that there is reason for cautious optimism. In this mouse model of PCOS, reproductive and neuroendocrine PCOS-like characteristics were recovered by intermittent therapy with the GnRH antagonist cetrorelix (Tata et al., 2018). Other innovative neuroendocrine therapies for PCOS try to reduce GnRH pulsatility by targeting upstream inputs within the GnRH neuronal network. These inputs are sensitive to the ovarian androgens, oestrogens, and progesterones that are generated. The population of neurons in the hypothalamus that co-express the neuropeptides kisspeptin, neurokinin B, and dynorphin are referred to as 'KNDy neurons,' and they are identified as being essential for the creation of GnRH pulses. This population of neurons is the best known therapeutic target for accomplishing this goal (Clarkson et al., 2017; Navarro, 2012). Dynorphin has an inhibiting effect on GnRH release, in contrast to the stimulating effects of kisspeptin and neurokinin B. Hypogonadal hypogonadism is caused by gene mutations that lead to the loss of function in KISS1R, which encodes the kisspeptin receptor, as well as TAC3 and TACR3, which encode neurokinin B and its receptor, respectively (de Roux et al., 2003; Seminara et al., 2003; Topaloglu et al., 2009).

MEDICATIONS AIMED TOWARDS TREATING INSULIN RESISTANCE

Both overweight and normal-weight women with PCOS have hyperinsulinemia and insulin resistance. Hyperandrogenism is further exacerbated by insulin excess, which decreases SHBG and increases testosterone bioavailability and ovarian androgen production. Alternative insulin sensitising agents, such as hHumanin analogues, sSodium glucose co-transporter inhibitors, and incretin mimetics, are being researched for the management of insulin resistance in PCOS due to metformin's lack of protection from cardiovascular risks and its adverse gastrointestinal side effects (Glendining & Campbell, 2023).

Humanin

Humanin is a peptide produced in the mitochondria that protects neurons, leukocytes, and gonad cells from the damaging effects of stress. Recent research has shown that people with PCOS who also have insulin resistance have lower levels of humanin expression in their ovarian follicular fluid and granulosa cells (Y. Wang et al., 2021).

Sodium glucose co-transporters (SGLT1, SGLT2)

Type 2 diabetes has been treated using SGLT2 inhibitors, a relatively new class of anti-diabetic medication. They decrease renal glucose absorption and increase urine glucose excretion to lower blood sugar levels, but they also promote weight reduction and enhance insulin sensitivity, making them a potentially useful alternative to insulin sensitising medicines for treating PCOS complications. Recent clinical trials comparing the efficacy of SGLT2 inhibitors with standard

metformin treatment for overweight/obese patients with PCOS indicate substantial benefits over standard metformin treatment, including significantly reduced body weight, decreased serum DHEAS, and fewer medication-related adverse effects (Cai et al., 2022; Javed et al., 2019). In a similar manner, women with PCOS who were treated with the SGLT2 inhibitor dapagliflozin for a period of 24 weeks saw a reduction in body weight, fasting glucose levels, and blood pressure, as well as a reduction in serum levels of total testosterone and free androgens, but a rise in SHGB levels (Elkind-Hirsch, Chappell, Seidemann, Storment, & Bellanger, 2021).

In contrast to SGLT2, which modulates glucose uptake in the kidney, SGLT1 mediates glucose uptake in the intestine. In a recent short-term (2-week) Phase 2 trial of licogliflozin (LIK066), a dual SGLT1/2 inhibitor, in women with PCOS, this dual treatment significantly reduced serum insulin and androgen levels compared to placebo (Tan et al., 2021).

Incretin Mimetics

Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) are examples of incretins, which are hormones produced in the intestine in response to food and which stimulate glucose-dependent insulin secretion. Inconclusive evidence exists as to whether incretin hormone levels are altered in PCOS; however, incretin mimetics such as the GLP-1 receptor (GLP-1R) analogues have demonstrated promise in the treatment of PCOS. In a clinical trial, the GLP-1R agonist Liraglutide reduced unbound androgens and body weight and enhanced insulin sensitivity in hyperandrogenic PCOS

women compared to placebo (Elkind-Hirsch, Chappell, Shaler, Storment, & Bellanger, 2022).

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CHAPTER XXII

POLYCYSTIC OVARY SYNDROME (PCOS) SURGERY: AN OVERVIEW

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1. Introduction

The most frequent reasons of ovulatory failure and the resulting infertility is polycystic ovarian syndrome (PCOS). It is characterised by the development of several small cysts in the ovaries, decreased ovulation function, androgen excess, obesity, hypersecretion of luteinizing hormone, and infertility as a relatively prevalent condition in women during their reproductive years. Ultrasonography or other imaging techniques are typically not required for diagnosis; a thorough history, physical examination, and simple laboratory tests are usually sufficient. The Rotterdam criteria (2003) state that polycystic ovaries, ovulatory dysfunction, and hyperandrogenism must all be present for a diagnosis to be made. The Androgen Excesses and PCOS Society (2009) states that the patient's hyperandrogenism must be combined with either polycystic ovaries or oligomenorrhea. Depending on the symptoms and desire to become pregnant, PCOS is needed to be treated on an individual basis. PCOS symptoms and any related negative effects can be treated with a variety of tools and drugs. Biopsy, multipunctures, laparoscopic laser, transvaginal natural orifice endoscopic surgery, laparoscopic ovarian drilling, transvaginal needle, Oophorectomy/ovarian ablation are major surgery options which are the subject of this overview study.

The development of several small cysts in the ovaries and a reduced ability to ovulate are two features of the polycystic ovarian syndrome (PCOS). Contrary to other types of anovulation that include ovarian dormancy or primary insufficiency, it is a complex disorder characterised by persistent anovulation and excessive ovarian activity.

According to recent studies, PCOS is linked to low-grade chronic inflammation and puts women at higher risk for non-alcoholic fatty liver disease. The cohabitation of insulin resistance and obesity is one explanation for the inflammatory and metabolic abnormalities linked to PCOS, but the excess testosterone is also a contributing factor. The idea that PCOS is a systemic syndrome is supported by recent findings regarding the modulation of hormones and cytokines in muscle and adipose tissue (Rocha et al., 2019). PCOS is a metabolic, reproductive, and psychological disorder that has effects across the lifetime and affects 5–18% of women. Numerous elements, including epigenetic and genetic vulnerability, ovarian and hypothalamic dysfunction, insulin resistance, excessive androgen exposure, and pathways related to obesity, contribute to the issue. Two of the three criteria—irregular cycles, hyperandrogenism (clinical or biochemical), and polycystic ovary morphology—must be present for a diagnosis to be confirmed using the 2003 Rotterdam criteria. Ovarian morphology is excluded due to low specificity, and both the hyperandrogenism and irregular cycle requirements must be present in teenagers. Four phenotypes are produced by the diagnostic criteria, and clinical characteristics vary widely. Manifestations often start in childhood and progress into adolescence and adulthood. A combination of medical management and lifestyle changes are used as treatment. With the goal of preventing excessive weight increase, limiting PCOS consequences, and achieving weight loss when necessary, optimisation of lifestyle involves a healthy, balanced diet and regular exercise. Metformin improves insulin resistance and metabolic characteristics, combination oral contraceptives, which control both hyperandrogenism and the

menstrual cycle, and, if necessary, anti-androgens, which treat refractory hyperandrogenism are among the medical care choices (Joham et al., 2022).

Some of the most confusing features of PCOS are its prevalence, diagnosis, aetiology, management, therapeutic practises, psychological problems, and prevention. Women with PCOS have a wide range of symptoms throughout their lives. Confirmatory PCOS-related data is provided by physical, biochemical, and radiographic assessments combined with medical history. The three defining symptoms of PCOS are anovulation, hyperandrogenism, and polycystic ovaries. Other prominent PCOS symptoms include metabolic problems, luetinizing hormone hypersecretion, hyperinsulinemia, insulin resistance, dyslipidemia, glucose intolerance, hirsutism, obesity, acne, diabetes mellitus type II, and infertility. Cardiovascular incidents, endometrial cancer, and psychological conditions including stress and despair are only a few examples of long-term problems. Over the past ten years, it has become more and more clear that PCOS patients require better clinical and therapeutic care. To reduce the severity of PCOS patients' clinical symptoms, there are numerous therapy options available. Every doctor should have the option to select the best appropriate protocol when it comes to PCOS and the potential for pregnancy. The use of specific biological markers, more accurate methods of measuring circulating androgens, awareness of the risks associated with PCOS, and, finally, phenotype-specific treatment approaches were the main strategies for better managing PCOS (Deswal et al., 2020).

Strong heritable factors contribute to PCOS. Key PCOS genes are regulated by DNA hypomethylation, and blood samples from women with PCOS as compared to healthy controls show changes in several of the differentially methylated genes. They propose methylome markers as a potential diagnostic landmark for the disorder and also identify prospective candidates for epigenetic-based therapy (Mimouni et al., 2021). The transmission of PCOS features to subsequent generations happens via an altered landscape of DNA methylation (Mimouni et al., 2021). The majority of patients will be able to get pregnant and have a live birth with the use of a "stepwise approach" to managing infertility in PCOS. 1. An appropriate lifestyle that includes nutrition and exercise for weight loss. 2. Drugs taken orally Clomiphene citrate (CC), a selective oestrogen receptor modulator, is one of the first-line oral medications. Letrozole (aromatase inhibitors) is the other oral first-line medication. A supplement to ovulation induction in patients with obesity and glucose intolerance is metformin (insulin sensitizers). 3. In cases of CC resistance or CC failure (no pregnancy after four to six ovulatory cycles), gonadotrophins are the second-line treatment. 4. For women with CC-resistant PCOS, laparoscopic ovarian drilling (LOD) may be utilised as a second-line treatment, especially if there are additional laparoscopic reasons, an elevated risk of multiple pregnancies, or a contraindication to multiple pregnancies. 5. If properly managed, in vitro fertilisation (IVF) has high success rates in treating PCOS-related infertility and may result in a lower rate of multiple gestations. In fact, while employing gonadotrophins in IVF, rigorous monitoring of controlled ovulation seeks to prevent multiple pregnancies (Lebbi et al., 2015).

In most PCOS patients, Ovulation induction surgery restores a woman's menstrual cycle and improves her endocrine profile. Seventy years after the first account of an effective surgical ovarian intervention in PCOS, the mechanism behind the recovery of endocrinological dysfunction is still a mystery. At the moment, surgical ovarian intervention of PCOS is rarely employed because adequate ovulation and pregnancy rates can be obtained with the help of gonadotrophins, metformin, and clomiphene citrate. Ovarian surgery becomes an option, though, for some women who are still anovulatory or who are unable to be adequately treated medically (Hendriks et al., 2007).

3. Laparoscopic wedge resection (Laparoscopic cystectomy)

Surgery to remove a triangle-shaped piece of tissue is known as a wedge resection. It can be used to remove a tumour or another type of tissue that needs to be excised and usually has a limited amount of surrounding healthy tissue. It just leaves a single stitch line as a remnant, is simple to repair, and does not significantly alter the form of the underlying organ. The first successful laparoscopic "wedge resection" technique for treating infertile PCOS women was described in 1935. It served as the sole treatment for polycystic ovary disease for a considerable amount of time. Despite these encouraging outcomes, the surgical method was outperformed by pharmaceutical therapy because of the increased risk of pelvic adhesions after surgery. When anti-oestrogen therapy (clomiphene citrate) was introduced and the positive outcomes of these therapies were made public, the surgical approach, which had the drawback of potentially causing peri-ovarian adhesion formation, was abandoned. Biopsy (Utsunomiya et al., 1990),

cauterization (Gjonnaess, 1994), laser (Ostrzenski, 1992), cauterization laser (Pellicer & Remohi, 1992), and coelio resection are some of the laparoscopic therapy options for polycystic ovarian syndrome. The use of these laparoscopic procedures for PCO cases that don't respond to medical treatment has been mentioned in various papers over the past few years.

3.1. Biopsy (Electrocauterization, Ovarian electrocautery)

In 1972, the first report on pregnancies that resulted from laparoscopic ovarian biopsies with cauterization using the Palmer forceps was published. Three problems related to the ovarian biopsy were found in the 778 instances described by Cohen (1989). Two of the ovarian haemorrhages had been difficult to coagulate episodes due to ovarian blood vessel damage. For haematocele, one case required an urgent laparotomy, whereas the other required a delayed laparotomy. The other issue was a bowel rupture brought on by an electric pulse, which occurred nine days after laparoscopy. An easy suture was used to treat it. Haemostasis could be achieved in all the other instances where ovarian haemorrhage occurred during the biopsy procedure by either cauterising or by applying pressure to the two sides of the biopsy using forceps. A straightforward depression on the ovary's surface was the typical biopsy manifestation. Adhesions were never seen on the biopsied zona (Cohen, 1996).

3.2. Multipunctures (Electrocauterization, Ovarian electrocautery)

In order to treat PCOS, Gjoannaess (1984) suggested laparoscopic multielectrocauterization. He had a 92% ovulation rate and a 69%

pregnancy rate. Ovulation was achieved in 92% of the whole series and pregnancy was achieved in 84% of the 252 PCOS patients treated with ovarian electrocauterization between 1979 and 1991, according to Gjoannaess (1994). Small scissors were suggested for cauterization by Greenblatt and Casper in 1987. Their method involved making 8–10 punctures on each ovary with a current of 4 amps until the cortex was penetrated. Using monopolar forceps and several punches, Sumioki et al. (1988) suggested doing multiple punch resection-cauterization on 6–10 surface follicles.

3.3. Laparoscopic laser

In laparoscopic laser drilling, a laser offers regulated power density, desirable depth of penetration, and predicted thermodamage to the tissues around it. Additionally, it might make adhesions less likely. Carbon dioxide (CO2), argon, YAG, and potassium titanyl phosphate (KTP) lasers have all been employed. Although using a laser gives surgeons more control over the sort of ovarian damage they might do, this does not seem to have any therapeutic benefits (Cohen, 1996). Translaparoscopic CO2 laser ovarian wedge excision was a method employed by Ostzrenski (1992). A 1 cm wide portion of the free ovarian surface was vaporised. In the 12 patients that were part of the study, he noted a 92% pregnancy rate and an 8% postoperative adhesion rate.

Gynaecological problems such as rupture, haemorrhage, and torsion might aggravate ovarian cysts (Balachandren et al., 2021). Depending on the type of cyst, its size, and imaging results, ovarian cyst therapy

might range from maintenance treatments to surgery. Due to the dangers of ovarian cysts existing, potential rupture, or cancer, laparoscopic cystectomy has emerged as the gold standard in the surgical management of persistent adnexal masses (Baekelandt, 2018). Ovarian reserves are so impacted by ovarian cystectomy. Gynaecological experts are concerned about the use of various surgical methods in this field because they cause ovarian tissue damage, which can worsen the injury to the surviving follicles. "Ovarian reserve" refers to the quantity of surviving oocytes and describes the quantity and calibre of ovarian follicles, as well as the ovary's functional capacity. Tests to determine ovarian reserve include measuring levels of anti-Mullerian hormone (AMH), estradiol, follicle-stimulating hormone (FSH), FSH/LH, luteinizing hormone (LH), and inhibin-B (Kostrzewa et al., 2019). The antral primary follicles' granulosa cells release AMH, a glycoprotein dimer. Ovarian reserve can be tested using serum AMH levels because they fluctuate very little throughout the course of the monthly menstrual cycle. On the other hand, compared to before surgery, there may be a considerable drop in AMH levels between the third and sixth months after ovarian cystectomy. For gynaecological researchers, the impact of variables including cyst size, pathology, and type of involvement (unilateral, bilateral) is an ongoing challenge (Mansouri et al., 2022).

4. Transvaginal natural orifice endoscopic surgery

A surgical procedure called transvaginal natural orifice transluminal endoscopic surgery of ovarian cystectomy enables the removal of ovarian cysts by accessing the peritoneal cavity vaginally. Transvaginal

natural orifice transluminal endoscopic surgery is a unique, minimally invasive method for performing ovarian cystectomies. It is still a novel strategy that needs more research. It may offer superior cosmetic outcomes and increased patient comfort (Baekelandt, 2018). The discipline of minimally invasive surgery has significantly advanced with the development of NOTES (natural orifice transluminal endoscopic surgery). The benefits of NOTES include superior cosmetic outcomes, a shorter recovery period following surgery, and a decrease in wound infections (Li & Hua, 2020).

5. Ovarian drilling

Ovarian drilling, which involves using laparoscopic tools to pierce or burn cysts in the ovaries, can help restore the hormone imbalance brought on by polycystic ovarian syndrome and help ovulation restart. There are two types based on the number of ovaries involved: 1) BLOD (Bilateral laparoscopic ovarian drilling), which involves drilling two ovaries, and 2) ULOD (unilateral laparoscopic ovarian drilling), which involves drilling just one ovary. The amount of tissue that is removed determines whether ULOD or BLOD is successful. Statistically significant increases in the rates of ovulation and pregnancy have been made with a thermal dosage of 1200 J in BLOD. Zakherah et al. (2011) shown that thermal doses adjusted to the ovarian volume can further improve these ovulation rates compared to the fixed dosage, but their levels reached up to 2160 J. Adhesions, particularly on the left ovary, a decreased ovary reserve as a result of tissue damage, the need for more stitches and greater heat doses are some of the negative effects of BLOD (Roy et al., 2009; Fernandez et al., 2011). As a result, a less

harsh LOD technique has been suggested (Sunj et al., 2013). The danger of ovarian tissue damage and post-operative adhesions are reduced as a result of unilateral treatment, which also stimulates activity in both ovaries. However, ULOD requires further evaluation (Roy et al., 2009) because no optimal dose has yet been shown to stimulate ovulation reliably, and it has not been adopted as a sustainable surgical option (Fernandez et al., 2011).

In terms of the method of accessing the ovaries, there are two methods: 1) laparoscopic and 2) transvaginal.

5.1. Laparoscopic ovarian drilling (LOD)

With the emergence of a minimally invasive technique called laparoscopic ovarian drilling (LOD), the surgical treatment of PCOS cases that were CC-resistant significantly improved. It is unknown if a common action is exerted by a direct effect on the ovary or through a systemic endocrine mechanism, and it is also unclear exactly how minor perforations using heat or a laser result in follicular expansion and ovulation. The most likely mechanism is that the thermal destruction of ovarian follicles and a portion of the androgen-producing stroma reduces local and serum androgen levels, restoring an intrafollicular environment more conducive to typical follicular maturation and ovulation, and leading to a subsequent increase in follicle-stimulating hormone (FSH) levels. Furthermore, it has been proposed that the release of a series of regional growth factors, including insulin-like growth factors that interact with FSH, after a surgically induced rise in ovarian blood in response to thermal injury

enables follicular development and eventual ovulation. The formation of "holes" in the polycystic ovary's extremely thick cortical wall and the drop in anti-Müllerian hormone (AMH) concentrations are two other potential explanations (Mercorio et al., 2022).

Prior to using gonadotrophins, patients' treatments begin with weight loss and CC. However, there is a significant risk of ovarian hyper-stimulation (OHSS) and multiple pregnancies when gonadotrophins are used. Following LOD, there is a lesser chance of multiple pregnancies than following gonadotrophin stimulation. So, before gonadotrophins, surgery with LOD may be an alternative to achieve normal ovulatory cycles. It was suggested as a less invasive alternative to bilateral ovarian wedge resection almost thirty years after Gjönnaess (1984) published the first report of LOD employing a unipolar electrode. Regarding the mechanism of action of ovarian drilling and the best and most affordable method for treating PCOS syndrome, there are still many questions that need to be resolved. The most likely mechanisms of action involve the removal of ovarian follicles and a portion of the ovarian stroma, which lowers serum levels of androgens and inhibin and raises FSH while restoring ovulation. A high delivery of gonadotrophins and post-surgical local growth factors is made possible by LOD, which could increase ovarian blood flow. It has also been proposed that LOD improves insulin sensitivity (Farquhar et al., 2012). Monopolar electrocautery (diathermy) or laser usage is a typical LOD method. Each ovary typically receives three to eight 600-800 J diathermy punctures, which in 74% of cases result in a subsequent normal ovulation within the next three to six months. According to

Farquhar et al. (2012), having more than eight punctures may result in more post-operative pelvic adhesions and a reduction in ovarian reserve. Later, ovarian drilling using various other minimally invasive procedures was described. Bipolar energy probes were suggested by some writers as a possible safer alternative to unipolar energy for LOD. The micro-laparoscopic ovarian drilling technique (MLOD) under local anaesthesia, which permits outpatient management without general anaesthesia, was described by other authors. Another method with outcomes similar to laparoscopy was described as fertiloscopy (transvaginal hydrolaparoscopy) (Pouly et al., 2013). With the same outcomes as a monopolar needle, laser was also tested for ovarian drilling during laparoscopy or fertiloscopy. There was no evidence of a significant difference in rates of clinical pregnancy, live birth, or miscarriage in clomiphene-resistant PCOS women undergoing LOD compared to other medical treatments, according to a systematic Cochrane review that included 25 randomised controlled trials of sub-fertile women with PCOS who underwent LOD to induce ovulation. This method is appealing and practical due to the decrease in the prevalence of multiple pregnancies in women who undergo LOD. According to Fernandez (2011), ovarian drilling results in the spontaneous restoration of fertility in 20–64% of PCOS-afflicted women who were previously infertile due to anovulation and who did not react to CC therapy. Ovarian drilling may be more effective in patients with high LH concentrations (>10 IU/l) and less than three years of infertility, among other conditions. However, there is conflicting evidence about the effects of additional variables as BMI, insulin resistance, and testosterone levels. In terms of ovulation

induction in PCOS-affected women, LOD does not perform better than CC. Furthermore, as a first-line method for anovulatory infertile patients, there is no appreciable difference in pregnancy and live birth rates per woman using LOD versus six cycles of CC. But LOD is the greatest option for inducing mono-ovulatory cycles with a greater pregnancy rate in women who have not been able to conceive after six to nine cycles of CC. According to Badawy and Elnashar (2011), the explanation is that LOD prevents CC's peripheral anti-estrogenic effects on endometrial and cervical mucus as well as the hypersecretion of LH that causes premature luteinization in response to CC. According to several studies, LOD before ART helps women who have previously had IVF cycles cancelled owing to OHSS risk or who have experienced OHSS during a previous treatment by lowering the risk of severe OHSS and increasing the "take home baby" rate. This observation might be explained by decreased ovarian blood flow and vascular endothelial growth factor (VEGF) levels following LOD (Mayenga & Belaisch-Allart, 2011). LOD is generally accepted to be a second-line treatment for PCOS patients, particularly for those who have CC resistance. The main advantages are a shorter gestation period and decreased dependence on ovulation stimulants. Additional benefits of this approach include increased comfort, cost effectiveness, and the potential for ambulatory performance. However, as a first-line treatment for PCOS, LOD's outcomes are not superior than those of CC (Lebbi et al., 2015).

In cases where medical therapy is ineffective, ovarian drilling is now accepted as a second-line therapy. In terms of live birth rates,

laparoscopic ovarian drilling (LOD), the modern equivalent of ovarian wedge resection, is thought to be beneficial for gonadotropin therapy without the iatrogenic complication concerns. After the completion of this treatment, ovarian reactivity to subsequent ovulation induction drugs is improved, and its endocrinal effects are longer lasting. However, traditional LOD should only be used in specific situations due to the potential hazards of iatrogenic adhesions and diminished ovarian reserve. Although their roles are still unclear and none of them have offered sufficient proof in terms of efficacy and safety, novel customised and mini-invasive ways have been offered to overcome these limitations. However, these approaches are still awaiting widespread approval (Mercorio et al., 2022).

Key factors to success in ovarian drilling are (Mercorio et al., 2022):

1) Infertility duration greater than three years, marked biochemical hyperandrogenism (free androgen index—FAI>15), high basal anti-müllerian hormone AMH (>7.7 ng/mL), obesity (BMI > 25), low basal luteinizing hormone (LH) (10 IU/L), and duration of infertility greater than three years should all be taken into consideration when choosing patients.
2) The method that has received the most recognition involves making four bilateral punctures at a depth of 3 to 4 m, each lasting 4 seconds at a power of 40 W (the rule of 4), and transferring 640 J of energy to each ovary.

3) To promote a quicker recovery and better cosmetic outcomes, a mini laparoscopy with a 5.0 mm laparoscope and accessory ports of 3 mm could be used while under regional anaesthesia.
4) The ovary needs to be gently pulled away from the gut and ureters before to the administration of energy.
5) To cool the peritoneal cavity and ovaries after heating lesions and lowering the possibility of post-operative adhesion development, up to 1000 mL of isotonic fluid should be used.

Despite the fact that ovarian diathermy's effects are temporary and should only be used on infertile women, many women report positive reproductive outcomes that last for several years due to repeated spontaneous ovulation and subsequent pregnancies rather than repeated cycles of ovulation induction (Debras et al., 2019). Prior to beginning assisted reproductive therapy, particularly in vitro fertilisation (IVF), which is regarded as an effective treatment option in anovulatory PCOS patients who are unable to conceive with ovarian drilling, the increased responsiveness of the ovary to CC or gonadotropin medical therapy after LOD failure can be of great assistance. Women with PCOS often experience more difficult stimulation than healthy women and frequently have a greater cycle cancellation rate as compared to normo-responders. According to reports, patients who had prior surgical therapy had a statistically significant decreased incidence of OHSS. A single LOD treatment produces multiple mono-ovulatory cycles, whereas a single course of gonadotropin therapy only produces a single ovulatory cycle with the associated cost of extensive monitoring. LOD is also significantly less expensive than ovulation induction with

gonadotropins. Those who conceive using gonadotrophins pay higher costs due to the higher prevalence of multiple pregnancies (Van Wely et al., 2004).

Ovarian drilling can be done using a laser or a diathermy needle, however the latter is the quickest and least expensive method. Using atraumatic forceps and a diathermy needle placed on the ovary's surface, the ovarian ligament grasps the ovary. Typically, a mix setting is utilised with a diathermy setting of 25 to 30 W. The needle is permitted to enter the ovarian tissue for 1 to 2 mm during the approximately 4-second activation of the diathermy. Drilling up to 10 holes that are spaced out across the ovary's surface is the goal. The ovary can frequently be moved with the diathermy needle if the current is briefly initiated while the needle is in contact with the ovarian surface, even though the target area first appears to be out of reach. In order to manipulate the ovaries and produce a more radial direction of travel for the needle, this causes the needle tip to adhere to the ovarian surface. It's crucial to prevent the ovary from coming into contact with the heated bowel. Saline lavage is recommended by some writers, while others advise merely holding the ovary outside the pelvis to allow it to cool naturally. Care must be taken to avoid the needle reaching the hilum of the ovary, which is vascular and can bleed profusely (Mane & Penketh, 1999).

5.2. Transvaginal needle

Patients with PCOS who are not responding to medication can undergo ovarian drilling, which can be done by invasive laparoscopic access or

less invasive transvaginal access. Women with polycystic ovarian syndrome and ovulation issues can have surgery with a transvaginal needle. To puncture or burn ovarian cysts with a transvaginal needle, the ovaries must be reached vaginally. In terms of pregnancy and live birth rates, laparoscopic ovarian drilling has shown clinical efficacy comparable to that of gonadotropins. Compared to other surgical ovulation induction techniques, ultrasound-guided transvaginal ovarian needle drilling is a new one. An ovum is released from the dominant follicle to the cavitas pelvis with the help of transvaginal ovarian drilling, which involves puncturing each ovary with a sharp needle and aspirating all visible tiny follicles. The levels of intraovarian androgen, inhibin B, serum androgen, luteinizing hormone (LH), and other steroid hormones rapidly and significantly fall after puncture and aspiration. A thicker ovarian surface that aids in follicular growth and ovulation, as well as adequate gonadotropin secretion and a rise in follicle stimulating hormone (FSH), are all brought about by the reduced peripheral testosterone to oestrogen conversion that results from this. The possible benefits of transvaginal ovarian drilling over LOD include lower costs, the ability to do the procedure as an outpatient procedure, and a decreased risk of surgical consequences, namely iatrogenic adhesions and early ovarian failure (Baradwan et al., 2023).

6. Oophorectomy/Ovarian ablation

Oopherectomy refers to the surgical removal of the ovaries. An oophorectomy may involve removing one or both ovaries. If one ovary is removed, it's called a unilateral oophorectomy, and if both ovaries are removed, it's called a bilateral oophorectomy. Oopherectomy is

usually performed as laparoscopic or open surgery. Open surgery involves removing the ovaries by making a larger incision below the abdomen. The postmenopausal age group of women favours this option. Endoloops on the pedicle can be used to carry out these surgeries. Tissue extraction bags can be used to reduce spillage. The posterior colpotomy can be used to remove big cysts and enlarged ovaries. Adhesiolysis must be carried out carefully and with respect for the ureter's path. Sutures, harmonic scalpels, monopolar or bipolar diathermy, or other techniques, can be used to regulate the infundibulopelvic ligament. If the fallopian tube is to be preserved, the ovarian ligament must be coagulated, divided, and the fimbriae must be removed from the ovarian surface. The ipsilateral ileac fossa port is used to separate the tissue after the suture has been severed, while applying pressure to the ovary to pull it medially. To prevent the ligature from slipping, it is crucial to leave some tissue distal to it (Mane & Penketh, 1999)

Ablation is the burning or destruction of ovarian tissue by methods such as laser, electric current, radiofrequency or hot water. There are two types, laparoscopic ovarian ablation and transvaginal ultrasound-guided ovarian ablation.

7. Conclusions

Ovarian drilling is a surgical treatment used on women with polycystic ovary syndrome and ovulation issues. It is performed laparoscopically, requiring only minor abdominal incisions, and uses a camera and surgical tools to view and treat the internal organs. Ovarian drilling,

which involves using laparoscopic tools to pierce or burn ovarian cysts, can help restore the hormone balance that polycystic ovary syndrome has disrupted and resume ovulation. For women who are resistant to medicine or who experience negative effects from medication, ovarian drilling may be a possibility. Although there is a potential that this approach will result in pregnancy, this is not a guarantee. In addition to reducing acne and hair development, ovarian drilling can reduce other polycystic ovary syndrome symptoms like irregular menstruation.

Laparoscopic cystectomy is a surgical procedure that removes ovarian cysts in polycystic ovary syndrome patients via small abdominal incisions, using a camera and surgical tools. In comparison to open surgery, laparoscopic cystectomy is less intrusive, quicker to recover from, and may help lower the risk of pain, irregular menstruation, infertility, and cancer brought on by polycystic ovary syndrome.

By entering the peritoneal cavity via the vaginal channel, the transvaginal natural orifice transluminal endoscopic surgery of ovarian cystectomy allows for the removal of ovarian cysts. Compared to a standard laparoscopy, this procedure is less intrusive, less uncomfortable, and results in a quicker recovery. Additionally, because it is administered vaginally, it can be used on women who have polycystic ovary syndrome or who may have a suspected ovarian tumour. It also leaves no markings on the abdomen. By entirely eradicating ovarian cysts, this procedure can aid in restoring ovarian function, preventing infertility, and lowering the risk of cancer. A small incision is made in the vagina to be used in this surgery, and a tube with a camera and medical tools is placed through it. This tube allows

for viewing of the ovaries and allows for burning or puncturing cysts. After the treatment is complete, the tube is taken out and the vaginal incision is sutured.

Women with polycystic ovarian syndrome and ovulation issues can have surgery with a transvaginal needle. To puncture or burn ovarian cysts with a transvaginal needle, the ovaries must be reached vaginally. Compared to other surgical techniques like laparoscopic cystectomy or ovarian drilling, this procedure is less intrusive, less unpleasant, and offers a quicker recovery. Transvaginal needles can be used to alleviate polycystic ovarian syndrome symptoms such irregular menstruation, hair growth, and acne as well as to help rectify the hormone imbalance brought on by polycystic ovary syndrome and restart ovulation. For this procedure, a small incision is made in the vagina and an ultrasound probe is inserted through this incision. With this probe, the ovaries are visualized and the cysts are punctured or burned. After the procedure is finished, the probe is removed and the vaginal incision is sutured.

Compared to surgical wedge resection, laparoscopic procedures are less expensive and carry a decreased risk of post-operative adhesions. Laparoscopic techniques have many benefits over gonadotrophin therapy for clomiphene resistant patients, including serial repetitive ovulation events, no increased risk of ovarian hyperstimulation or multiple pregnancies, and a lower incidence of spontaneous abortion. However, these procedures should not be thought of as the first line of treatment for the anovulatory patient with PCOS, for whom clomiphene citrate remains the preferred mode of therapy.

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CHAPTER XXIII

PCOS AGING AND MENAPOUSAL PROCESS

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Since clinical and biochemical findings change with age, it may become difficult to diagnose polycystic ovary syndrome (PCOS) in the perimenopausal period (Believer et all.,2018). There are noticable decrease in androgenic hormone production in women with age, but this decrease is observed more in women without PCOS (Winters et all., 2000). A decrease in antimullerian hormone (AMH) and ovarian volume is observed with menopause (Brown in et all., 2011). Climacteric symptoms are less common in postmenopausal women with PCOS, whereas hirsuitism is more common (Schmidt et all., 2011).

As the AMH level decreases, the percentage of women with polycystic ovarian morphology begins to decrease from the age of 30. It's the same with non PCOS; ovarian volume increases up the age of 30 years, a great decrease is observed between the ages of 30-50 years (Pavlik in et all., 2000). Conflicting results have been demontsrated in studies on the change ovarian volume and number of follicles according to age in women with PCOS (Liang, et all,. 2011- Panidis in et all,. 2012). In addition to studies showing that there is no correlation between them, Carmina et al. showed a decrease in ovarian volume (Carmina et all,. 2012). In the study of Alsamarai et al. (Alsamarai in et all,. 2009). A significant decrease in ovarian volume and follicle number has been shown in women over the age of 40. In the study by Panidis et al,. (panidis in et all,. 2012), decrease in the follicles number was observed with advancing age, but no change in ovarian volume was observed.

Antimullerian hormone has been proposed as a strong marker for polycystic ovary due to its strong correlation with follicle number

(Fong in et all,. 2015). Actually, studies have shown that decreased AMH levels in PCOS are related to ovarian volume and follicle number.

The PCOS phenotype begins to improve as regular menstrual cycles occur, ovarian volume and follicle number decrease, and serum androgen levels decrease with age (Helvaci & Yildiz., 2020) In this context, a long-term study showed that the frequency of more severe phenotypes in women with PCOS decreased around the age of 40. But, it is unclear whether the improvement in the PCOS phenotype during the perimenopausal and postmenopausal period is associated with a reduction in the long-term health risks associated with PCOS.

Metabolic and endocrine problems during this period, begin to take precedence over gynaecological problems. The risk of insulin resistance (IR) is higher in women with PCOS, whether they are obese or not than in controls of the same age group and weight (Lim at all., 2012), and in this context, the risk of developing type 2 diabetes (T2DM) increases in individuals with PCOS. Metabolic syndrome, increased total cholesterol, elevated triglycerides, increased insulin secretion and high blood pressure are more predominant in women with PCOS in this age group.

İncidence of heart disease may also increase due to increased incidence of obesity, insulin resistance, impaired glucose intolerance and dyslipidaemia (Believer et all.,2018). However, no clear results have been shown as to whether PCOS status alone increases cardiovascular mortality (Fauser in et all,. 2012). Nonalcoholic fatty liver disease (NAFLD), mood disorders (depression and anxiety) and eating

disorders are more common in older PCOS patients than in women of the similar body mass index (BMI) (Gutierrez-Grobe in et all,. 2010- Veltman-Verhulst ,. 2012). The incidence of sleep apnoea is also increased due to obesity, androgen increase and insulin resistance. After the diagnosis of PCOS is confirmed, it is recommended to conduct a cardio - metabolic risk assessment, which includes oral glucose tolerance test (OGTT), blood pressure monitoring, BMI calculation and fasting lipid levels . In case of impaired glucose tolerance test, a type 2 diabetes risk assessment should be performed (Believer et all.,2018).

PCOS and Long-Term Complications

Obesity

Increased BMI is an valuable finding in postmenopausal women. Current studies suggest that weight gain in midlife is primarily influenced by ageing, but shows that hormonal changes during the menopausal transition are significantly associated with body changes in favor of abdominal obesity (Davis et all,. 2012). Accordingly, it is suspected that obesity rates of visceral origin will increase especially for women with PCOS who enter menopause. Studies conducted in older women previously diagnosed with PCOS shows an increase in the incidence of overweight/obesity and waist circumference (Meun in et all,. 2020- Wild et all,. 2020).

When we look at the literature, PCOS are more prone to obesity after menopause than control groups (Echiburú in et all,. 2016).

Impaired Glucose Metabolism and Insulin Resistance

In a study, higher fasting blood glucose levels and a higher prevalence of T2DM were observed in 70-year-old women with a previous diagnosis of PCOS compared to controls of similar age (Meun, C in et all,. 2018). Polycystic ovary syndrome is known as a high risk factor for T2DM (Davidson et all,. 2021). Supporting studies show that the age-standardized prevalence of T2DM is higher in postmenopausal women with PCOS (Gambineri in et all,. 2012).

Dyslipidaemia

In a study involving PCOS and non-PCOS women with similar BMIs at approximately 70 years of age, higher triglyceride levels were found in women with PCOS (van der Ham et all,. 2022). Meun et al. also showed that triglyceride levels increased in women with PCOS at approximately 70 years of age (Meun, C in et all,. 2018). However, there are some studies showing that lipid levels are similar between the two groups (Merz in et all,. 2016). In the study of Wild et al. organised according to BMI, higher serum cholesterol levels were shown.

When follow-up studies with conflicting results are analysed, it is a controversial issue whether women with PCOS have unfavourable lipid profiles after menopause.

Hypertension

In a long follow-up study, It was found that the prevalence of hypertension in PCOS at the age of 70 was approximately 2 times higher than in the control group (Schmidt et all,. 2011). In studies on

women with PCOS in the menopausal transition period, the results regarding the prevalence of hypertension compared to those in the control group differ depending on BMI (Pinola in et all,. 2017-Louwers & Laven,. 2020). However, a case-control study showed a nearly two-fold increase in hypertension in middle-aged women (Meun, C in et all,).

Metabolic Syndrome

In a study comparing PCOS and control groups with an average age of 50 in terms of age and BMI, the prevalence of metabolic syndrome (25.0%) was found to be higher than controls (17%) (Schmidt et all). However, the fact that only 16% of the women in this study were in the postmenopausal period showed that more studies are needed to support the result. In the study by Pinola et al., a two-fold higher prevalence of metabolic sen drom was found in patients older than 39 years compared to the control group (Pinola in et all,. 2017), and some study suggested that only hyperandrogenism was independently associated with metabolic syndrome (Polotsky et all,. 2012).

Malignancy

Because of long-term exposure to unmet estrogen due to chronic oligo- or anovulation, women with PCOS are at increased risk for estrogen-dependent cancers such as endometrial, ovarian and breast cancers. Conditions that pose a high risk for these cancers, such as type 2 diabetes, obesity, nulliparity, and advanced age at first birth, are also common in women with PCOS (Dumesic & Lobo,. 2013). The incidence of these cancers increases with age and women with these

cancers are generally in the postmenopausal period (Cancer Research UK ,. 2020) therefore, care should be taken in the gynecological evaluation of women with PCOS during menopause. Current data about the relationship between PCOS and cancer are mostly related to endometrial cancer (EC). In the study of Barry et al., it was found that the risk of EC increased 2.8 times in women with PCOS (Barry et all,. 2014). In another retrospective study, it was reported that endometrial cancer increased 5.3 times in patients with PCOS (Helvaci & Yildiz., 2020). Similarly, in the study by Gottschau et al., a 4-fold higher risk of EC was found (Gottschau et all, 2015). When the studies are evaluated, a relationship can be established between menopause and EC. The results regarding ovarian cancer are controversial.

PCOS is a syndrome that affects millions of women worldwide and can be accompanied by metabolic, endocrine and reproductive problems. Hypertension, obesity, diabetes and malignancies, especially endometrial cancer, increase with ageing. Studies will continue to examine the effects of PCOS and ageing.

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CHAPTER XXIV

POLYCYSTIC OVARY SYNDROME (PCOS) AND ADIPOKINES

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INTRODUCTION

It is known that there is a connection between metabolism and reproductive functions. Adipokines are biologically active proteins that secreted by white adipose tissue. Interest in adipose tissue increased with the discovery of the hormone leptin in the mid-1990s. After the discovery of leptin, it came clear that adipose tissue is the main energy force moreover it is an important endocrine organ that could regulate the whole body energy homeostasis (1). Adipokines act on different parts of the human body, regulating and controlling glucose and fatty acid metabolism, energy expenditure, inflammatory response, cardiovascular function, reproduction, and other natural processes over the entire body or locally. Numerous studies have described and bandied the pivotal roles of adipokines in several female reproductive pathologies like polycystic ovary syndrome and gestational diabetes mellitus, preeclampsia and intra-uterine growth retardation (2). There are numerous studies that investigate adipokine levels, and pathways. A meta-analysis published in 2021 including of 71 studies shown that non-obese PCOS cases have significantly advanced levels of Chemerin, Leptin, Resistin, and Visfatin but a significantly lower circulating level of Adiponectin when compared with non-obese healthy controls (3).There is a vast and expanding universe of exploration interested in the part of adipokines in the development of PCOS.

ADIPONECTIN

Adiponectin is the most abundantly secreted adipokine by the substantially white adipose tissue, to travel through the blood (4). It is a

member of a protein family (5). Secreted by adipocyte as a metabolic messenger, Adiponectin is involved in the pathophysiological processes of numerous diseases, inhibiting tumor cell growth and metastasis through anti-proliferation and induction of apoptosis (6). Not only Adiponectin but also its receptors (AdipoR1 and AdipoR2) are present in human ovarian cells (oocytes, granulosa cells, follicular membrane cells, and cumulus cells) and human follicular fluid (7). Adiponectin is also known to be expressed in the hypothalamus and pituitary gland, indicating its possible part in modulating the central reproductive endocrine axis. (8).

Adiponectin levels were found to be significantly dropped in women with PCOS and in obese women without PCOS as compared with healthy slim women (9). In addition, Adiponectin concentrations were lower in the non-ovulating PCOS cases than in the regular ovulating PCOS cases, indicating its important part in ovulation disorders of PCOS (10).

CHEMERIN

Chemerin was first discovered in 1997 while studying psoriasis. In 2003, the ligand was formally named Chemerin, which turned out to be an adipokine. In adipose tissue, chemerin is generally expressed within mature adipocytes (11). Chemerin gene consists of five coding exons and located on chromosome 7 in humans. Chemerin receptors are the following three: chemokine-like receptor 1 (CMKLR1), G protein-coupled receptor 1(GPR1), and CCRL2, though binding G proteins to

perform their physiological functions (12). Chemerin has been found to have an important role in obesity and type 2 diabetes. It also participates in multiple illness, such as autoimmune diseases, urinary diseases, digestive diseases, and psychiatric diseases, by regulating blood pressure, inflammation, immune response, fat cell differentiation, and carbohydrate metabolism (13).

Chemerin is expressed in basal cells of the human uterus, stromal cells, and extravillus trophoblast cells and the human placenta (14). Chemerin and CMKLR1 play an active role in human granulosa cells (15). Local insulin resistance exists in granulosa cells of human ovary from PCOS cases. Inordinate insulin in serum can promote Chemerin production, and PCOS cases have elevated concentrations of Chemerin as compared with non-PCOS cases. Follicular fluid and luteinized granulosa cells of PCOS cases with insulin resistance have higher Chemerin levels, which can be induced by over-expressed insulin (16). This is a causal nexus between Chemerin and insulin resistance.

Macrophages play a crucial part in the inflammatory state and clearance of senility and apoptotic cells. Hyperandrogenemia in PCOS cases leads to increased Chemerin concentrations in the ovaries. In rats treated with dihydrotestosterone, experimenters demonstrated that high concentrations of Chemerin as a ligand for CMKLR1-expressing monocytes in the blood resulted in local ovarian inflammation, leading to granulosa cell apoptosis, follicular growth arrest, and anovulatory infertility (17). Additionally, a retrospective study showed that serum Chemerin level could reflect the seriousness of ovarian polycystic

changes a retrospective study showed that serum Chemerin level could reflect the seriousness of ovarian polycystic changes (18). All these studies demonstrated a relationship between Chemerin and follicular dysplasia in PCOS cases, but the underlying mechanism needs to be further studied.

LEPTIN

Leptin was discovered as an adipokine in 1994, substantially coming from the white adipose tissue. Leptin decoded by a gene on the chromosome 7 in humans. Leptin receptor, a member of the class I cytokine receptor family and it's decoded by diabetes (db) gene (19). Leptin is binds substantially the Leptin receptor to spark Janus kinase signal transduction transcriptional activator signal(JAK- STAT) pathway to regulate food input and energy homeostasis (20). It also participates in physiological conditioning similar as immune response, neuroendocrine response, systemic inflammatory response, and reproductive function.

Leptin regulates GnRH secretion through neurons, therefore playing a part in the initiation of puberty and periodic secretion of Gn even though there's no Leptin receptor in GnRH neurons (21). Elevated Leptin concentrations in follicular fluid is a sensitive marker of anovulatory fertility diseases by comparing the concentrations of Leptin in follicular fluid in fertility diseases with different etiologies (22). A meta- analysis found that the circulating Leptin concentrations innon-obese PCOS cases was significantly advanced than that in obese PCOS cases (3). The relation between homeostatic model assessment-

insulin resistance (HOMA- IR) and serum Leptin concentrations has also been illustrated. Insulin has been shown to enhance Leptin gene expression and elevate circulating Leptin concentrations (23). Insulin resistance leads to increased insulin content, which may induce the white adipose tissue to secrete further Leptin to share in the development of PCOS. Leptin plays a part in the circumstance and development of PCOS by regulating the reproductive endocrine axis and local steroid production of ovary as well as sharing in insulin resistance.

One of the major problems in PCOS cases is obesity. Studies have shown that hyperandrogenism may increase feeding and lead to obesity by suppressing Leptin levels in the cerebrospinal fluid therefore inhibiting Leptin signaling in the hypothalamus in a rat model(24).

OMENTIN

Omentin is a new adipokine. Omentin was first linked from the human omental adipose tissue (25). The human Omentin gene is located on chromosome 1q21.3. Visceral adipose tissue rather than subcutaneous adipose tissue frequently expresses Omentin-1 preferentially and abundantly (26).

Omentin is a secretory adipokine, and Omentin plays a positive organizing role in, insulin resistance, inflammation, and regulation of endothelial function (27).

A meta-analysis demonstrated that significant low levels of Omentin in cases with PCOS (28). In 2014 Cloix et al. identified Omentin

expression in human ovarian granulosa cells (29). They found analogous concentrations of Omentin in plasma and follicular fluid in control cases but significantly advanced levels of Omentin in follicular fluid than in plasma in cases with PCOS. They also showed the function of human granulosa-lutein cells to secrete Omentin under insulin stimulation. Another article revealed Omentin expression was low in the omental adipose tissue of women with PCOS and suggested that insulin can reduce Omentin expression in a dose-dependent manner (30). A case-control study showed that after conforming for BMI, Omentin concentrations in PCOS individuals with IR were lower than in those without IR. Omentin was also negatively correlated with BMI, HOMA-IR, and fasting insulin (31).

VEGF plays an important part in polycystic-like changes in ovary. Tan et al. found that serum VEGF levels were elevated in PCOS cases and dropped with the reduction of Omentin levels after metformin treatment (32). This study verified that Omentin may play a part in inhibition of polycystic ovary morphology (PCOM) changes.

RESULT

The diagnosis of PCOS, is still controversial and its pathogenesis is still unclear. Adipokines impact the pathological process of PCOS due to their important places in energy metabolism, inflammation, insulin resistance, cell aging and apoptosis. Existing studies have verified that several adipokines are differentially expressed in populations with and without PCOS and are associated with ovarian angiogenesis, steroid

hormone product, follicular development and granulosa cell apoptosis. Nevertheless, most studies are limited to describing the superficial correlation rather than expounding the underlying mechanism, for which there is still much to be explored.

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CHAPTER XXV

PCOS AND AMH

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1.Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among reproductive-aged women and affects 10–15% of them (Neven, A.C.H; Laven, J; Teede, H.J; Boyle, J.A.;) (Bozdag, Mumusoglu, Zengin , Karabulut, & Yildiz). Women may present with reproductive, endocrine (menstrual dysfunction or hyperandrogenism), and/or metabolic symptoms which can be vary. One of proposed mechanisms for hyperandrogenism is follicle maturation abnormalities (Lv, et al., 2020). The growing follicle does not progress to the dominant follicle, and as a result, polycystic ovarian morphology is seen on ultrasonography.

PCOS is specified by an increased number of follicles at all growing stages, mainly seen in the preantral and small antral follicles and an increased serum level of Anti-Müllerian Hormone (AMH). Between strong correlations of AMH and PCOS is based on secretion mechanism AMH. Anti-Müllerian hormone inhibits the recruitment of primordial follicles out of the resting oocyte pool and may suppress follicle-stimulating hormone (FSH) action contributing to ovulatory disturbances (Lv, et al., 2020), (Alebic, Stojanovic, & Dewailly, 2018). AMH expression continues until follicles reach approximately 8 mm in diameter, and expression is deficient in larger antral follicles. Consequently, there is a good correlation between AMH and antral follicle count (AFC) (Dewailly, et al., Update 2014), (Balen, Laven, Tan, & Dewailly, 2003), (Eilertsen, Vanky, & Carlsen, 2012).

Accordingly, AMH has been proposed as a marker of polycystic ovary syndrome and a substitute for AFC in diagnosing PCOS, especially when the ultrasound criteria remain controversial (Balen, Laven, Tan, & Dewailly, 2003).

A variety of cutoff values of AMH have been proposed, but sensitivity and specificity can be change, the optimal threshold is unknown. This chapter indicate the relationship between AMH and PCOS and to describe the importance.

2. Physiology of AMH

AMH(also Müllerian inhibiting substance-MIS) is a homodimeric glycoprotein belonging to transforming growth factor- β (TGFβ) superfamily (Lv, et al., 2020), (Dąbkowska-Huc, Cygal, & Skałba, 2008) (Silva & Giacobini, 2021).

AMH is released both in women in the ovaries and in men,in the testicles.AMH has a important role in gonadal sex differentiation prenatally by suppressing the development of the Mülleran ducts in males. In women, AMH production starts from 36^{th} post conception week. Then, after an impermanent neonatal peak, AMH levels remain low until puberty. Rising AMH serum levels to a plateau occurs in adolescent girls. Decline stars after the mid-20s and AMH serum levels eventually become undetectable several years before menopause (Lv, et al., 2020). AMH is released by granulosa and theca cells in primordial follicle albeit at low levels. Changes in AMH even precede modifications in FSH (follicle-stimulating hormone), inhibin B serum

levels, and antral follicle count. AMH secretion decreases significantly before menopause due to depletion of the follicle pool (Dąbkowska-Huc, Cygal, & Skałba, 2008). The serum AMH concentration reflects the ovarian follicle pool with a strong dependence on the number of antral follicles in the early follicular phase of the menstrual cycle (Dumont, Robin, & Dewailly, 2018). In folliculogenesis, AMH inhibite of primary follicle recruitment thus inhibition of selection from a pool of small antral follicles through gonadotropin recruitment (Lv, et al., 2020), (Dąbkowska-Huc, Cygal, & Skałba, 2008). Low antral follicle count may result in low AMH blood levels. AMH levels does not effect menstrual cycle phase. Therefore, blood sample be able to assess on any day of menstrual cycle.

AMH may attenuate FSH stimulation of follicle growth and decrease aromatase enzyme activity, thereby inhibiting estradiol production. Elevated AMH is likely detrimental to the process of follicle development and may contribute to the androgen dominant milieu detected in the follicles of women with PCOS by reducing the rate of conversion of androstenedione and testosterone to estrone and estradiol, respectively.

AMH is considered a useful marker of ovarian reserve, and even clinical outcome of IVF. The main advantage of measurement of AMH levels may be based of their low inter- and intracycle variability. Therefore, AMH levels could be used as a menstrual cycle independent marker. AMH is superior to age and FSH levels for estimation of ovarian reserve.

3.AMH in Pathogenesis and Treatment of PCOS

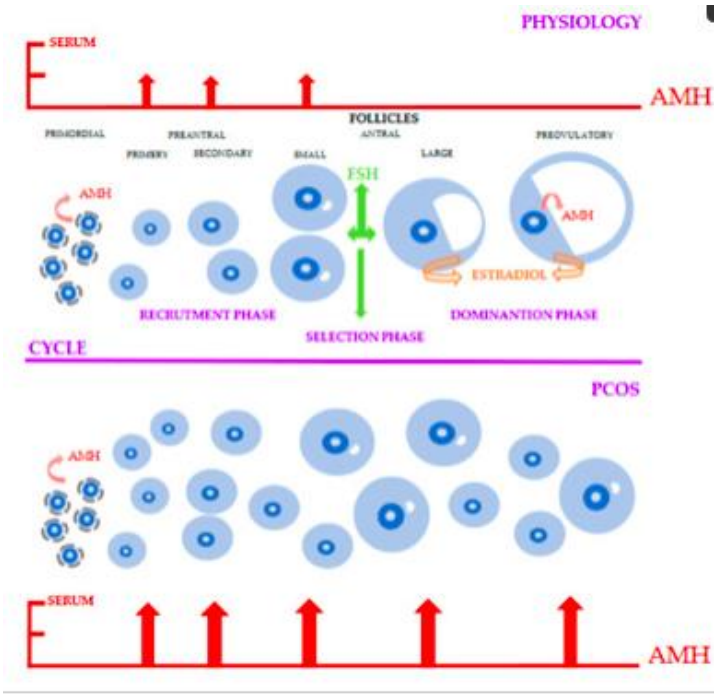

Figure 1. The roles of AMH (Anti-Müllerian Hormone) in PCOS (Polycystic Ovary Syndrome). In the physiological cycle, during the FSH (Follicle Stimulating Hormone) independent phase, AMH expression is lower in activated primordial follicles and highest in preantral and small antral follicles. In the FSH dependent phase, the expression of AMH is blocked. However, lower expression of AMH is observed in the preovulatory follicle. Therefore, the absence of AMH leads to an increased Estradiol level in antral and preovulatory follicles. In PCOS, the expression of AMH increases twofold, leading to an increased number of recruited follicles. In addition, such a high level of AMH reduces FSH expression and Estradiol synthesis, thereby blocking the selection phase and thus the formation of a preovulatory follicle. (Teede H, Misso M, Tassone EC, Dewailly D, Ng EH, Azziz R, Norman RJ, Andersen M, Franks S, Hoeger K, Hutchison S, Oberfield S, Shah D, Hohmann F, Ottey S, Dabadghao P, Laven JSE).

PCOS was defined by the Rotterdam Consensus Group and diagnosed based on hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology on ultrasonography. The data suggest that polycystic ovarian morphology (PCOM) may be a result of hyperandrogenism, so a revision of the diagnostic criteria for PCOS was suggested.

(Dewailly, Lujan, & Carmina) demonstrated that the serum concentration of the anti-Müllerian hormone (AMH), a peptide synthesized by the granulosa cells of follicles, is correlated with an increased number of follicles. They suggested that excessive number of follicles or high AMH concentrations may reflect the effect of intraovarian androgens disturbing the folliculogenesis in PCOS and thus could be used as "surrogates for classical hyperandrogenism markers.

Recent developments in ultrasonography have increased the number of follicles that can be counted; therefore, the number of women diagnosed with PCOM increased. Compared to women with PCOM, fewer women without PCOM have hyperandrogenemia or related problems and menstrual irregularities. Serum AMH concentration has been suggested as a replacement for an increased AFC and as a predictive marker of PCOS. The inhibitory effect of AMH on FSH function is believed to be one of the factors that causes anovulation in women with PCOS.

They also concluded that patients with PCOS phenotype A (the presence of all three Rotterdam criteria) were at a higher risk of OHSS, and these patients had higher serum AMH concentrations than those with other phenotypes.

(Namli Kalem, Kalem, & Gürgan, 2016) lists high AMH concentrations as a risk factor for OHSS that are related to the patient. (Sahmay, Atakul, & Oncul, 2013) and (Jamil, AS; Alalaf, SK; Al-

Tawil, NG, 2016) reported similar results regarding the AMH concentrations in PCOS phenotypes.

Researchers worldwide have suggested various cut-off levels for the serum AMH concentration. The cut-off levels varied among different ethnic groups.

Given the challenges with ultrasound in diagnosis of PCOS, including in the years after menarche, serum Anti-Müllerian Hormone (AMH) has been proposed as an alternative marker of ovulatory dysfunction in PCOS. AMH is a polypeptide of the transforming growth factor beta (TGF-β) family solely secreted by granulosa cells of the preantral and small antral ovarian follicles. Serum AMH levels are significantly higher in women with PCOS compared with normal ovulatory women (El-Mazny & Abou-Salem, 2013), (Vaiarelli, et al., 2016). Strong correlations have been demonstrated between circulating AMH levels and antral follicle count on ultrasound in PCOS. AMH may also provide insight into the pathogenesis of PCOS and the different phenotypes. However, current literature reveals significant heterogeneity and the diagnostic value of serum AMH remains far from clear.

One study included 179 women (59 PCOS and 120 no PCOS-controlled group) has been evaluated associations of AMH levels with in vitro fertilization (IVF) outcomes in PCOS patients. This study result that median serum follicular fluid AH and antral follicle count (AFC) and retrieved oocyte numbers were higher in PCOS patients than in

control group (Chen, et al., 2017). AMH levels correlated with AFC in PCOS patients.

Although serum AMH levels in adolescent and adult women with both PCOM and PCOS are significantly higher than those without these features in all studies, there is considerable overlap. A specific threshold of AMH in PCOS and PCOM is therefore very challenging. Heterogeneity between studies relates to assays, life stage and phenotypes studied. Another key contributor is the lack of well-defined populations including variable ultrasound criteria to establish PCOM and the criteria used to define controls.

4.Conclusion:

Serum AMH levels should not yet be used as an alternative for the detection of PCOM or as a single test for the diagnosis of PCOS. Many studies find that sensitive and specific cut off values AMH concentration for PCOS however it needs more studies to consider as a diagnostic criteria. Also, we need to big population studies to confirm. At this time, AMH assays are limited by the absence of an international standard; AMH is not currently part of the laboratory evaluation of PCOS. However, clinicians could use AMH and PCOS correlation along with Rotterdam criteria.

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CHAPTER XXVI

EFFECT OF THE BRAIN ON THE PATHOGENESIS OF POLYCYSTIC OVARY SYNDROME

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common and complex endocrine disorder affecting 5 to 20% of reproductive-born females and is an important cause of hirsutism and anovulatory infertility (Azziz et al. 2016). PCOS has gone bankrupt with many metabolic burdens, such as glucose intolerance, diabetes, dyslipidemia, surgery, hepatic steatosis, overweight, and various key markers.

According to the Rotterdam criteria, women must distinguish three main features for PCOS to be involved: 1) oligo- or anovulation, 2) clinical and/or biochemical hyperandrogenism, and 3) polycystic ovaries (The Rotterdam ESHRE/ASRM, 2004). Nonetheless, since alternative underlying causes like congenital adrenal hyperplasia, tumors that produce excessive androgens, and hyperprolactinemia can likewise result in limited ovulation and/or elevated androgen levels, these factors must be systematically ruled out. Consequently, arriving at a diagnosis of PCOS invariably involves excluding these alternative possibilities. Presently, there remains no definitive cure for PCOS due to the intricate and diverse nature of its symptoms, compounded by the fact that the root cause of the condition is still unidentified.

It is widely believed that the reproductive irregularities observed in women with PCOS stem from elevated levels of androgens and luteinizing hormone (LH) (Berga and Yen, 1989; De Vane et al., 1975; Vane et al., 1970). Females diagnosed with PCOS demonstrate elevated basal LH levels and an augmentation in LH bursts (Berga and Yen, 1989; Kazer et al., 1987), collectively contributing to the abnormal

elevation of LH levels. LH stimulates androgen production by ovarian theca cells. As a result, affected ovaries secrete elevated levels of androgens. A substantial number of PCOS patients also exhibit escalated luteinizing hormone (LH) secretion (Rebar et al., 1976). This could potentially be a result of heightened pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypophysiotropic GnRH neurons situated in the rostral forebrain (Pastor et al., 1998; Moore and Campbell, 2007). In comparison to women without PCOS, those with PCOS necessitate higher levels of estradiol and progesterone to effectively suppress the pulsatile release of LH (Pastor et al., 1998; Chhabra et al., 2005; Daniels and Berga, 1997). This observation indicates a deterioration in the ability of steroid hormones to curtail the activity of the GnRH/LH pulse generator.

The release of GnRH from the brain is a highly intricate process, finely tuned by the interplay of both neural and endocrine factors. This dynamic interplay collectively determines the timing and intensity of GnRH secretion. Gaining insights into the interplay between PCOS and the central nervous system holds the potential to yield more potent strategies for the management and treatment of this condition.

The arcuate nucleus has been suggested to be the main area in the brain associated with reproductive defects of PCOS in animal models. It is thought that gamma-aminobutyric acid (GABA) neurons in the arcuate nucleus and kisspeptin/neurokinin B/dynorphin neurons are responsible for the excessive androgen effects and may be a possible contributor to the deterioration of steroid hormone feedback to GnRH neurons in

PCOS models (Ruddenklau and Campbell, 2019; Walters et al., 2018; Coutinho and Kauffman, 2019).

Numerous clinical investigations have indicated the neuroendocrine underpinnings of PCOS, showcasing a notable connection between PCOS and psychiatric and neurological disorders. Notably, there exists an increased prevalence of PCOS in individuals diagnosed with bipolar disorder (Qadri et al., 2018). This association is thought to be a consequence of disruptions in neurotransmitter balance impacting the neuroendocrine axis governing reproductive functions. Similarly, women affected by epilepsy demonstrate an elevated occurrence of PCOS (Herzog et al., 1984; Herzog et al., 1986). This connection is linked to transient surges in LH, FSH, and prolactin levels, indicative of altered hypothalamic-pituitary functionality, which could potentially contribute to the development of PCOS (Dana-Haeri, 1983). Furthermore, the impact of valproate, a medication utilized for epilepsy treatment, merits consideration. Valproate functions by augmenting GABA levels and can modify neuron firing through inhibiting voltage-gated ion channels (Ghodke-Puranik et al., 2013). Consequently, modifications in GABA levels and their repercussions may directly or indirectly influence the hypothalamic-pituitary-gonadal axis. When all these interconnected associations are considered collectively, they further underscore alterations within the neuroendocrine axis as a potential contributor to the onset of PCOS.

PATHOPHYSIOLOGY AND INFLUENCE OF THE BRAIN

Gonadotropins

In PCOS-afflicted women, irregular gonadotropin secretion patterns distinguish the absence of ovulation. More precisely, the modified pulsatile release of gonadotropin-releasing hormone (GnRH) results in an imbalanced production of luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) (Hayes et al., 1998; Waldstreicher et al., 1988). Whether hypothalamic dysfunction serves as the primary instigator of PCOS or stems from disrupted steroid feedback remains an unresolved question. In both cases, serum LH levels are elevated; approximately 50 percent of affected women experience clinically elevated levels (van Santbrink et al., 1997). Similarly, approximately 60 percent of patients have high LH: FSH ratios exceeding 2:1 (Rebar et al., 1976). A noteworthy attribute of PCOS is the elevated serum LH: FSH ratio, a distinguishing factor. This phenomenon is attributed to heightened transcription of GnRH in the hypothalamus and GnRHR in the pituitary (Kauffman et al., 2015). Furthermore, through the use of immunohistochemistry and in situ hybridization, multiple investigations have demonstrated the expression of various neurotransmitter and neuropeptide receptors within GnRH neurons. These components directly regulate the release of GnRH, LH, and FSH (Smith and Jennes, 2001).

SEROTONIN

Serotonin: The impact of serotonin on GnRH neurons demonstrates a two-fold nature. Activation of the 5-HT2A receptor stimulates GnRH neuronal activity through the involvement of PKC (protein kinase C). Conversely, activation of the 5-HT1A receptor hampers GnRH neuronal firing by engaging adenylate cyclase (De Vivo and Maayani, 1986; Bhattarai et al., 2014). In the context of PCOS, the heightened release of GnRH and LH might be attributed, at least partially, to a decrease in the inhibitory influence of serotonin on GnRH.

CATECHOLAMINE

The influence of catecholamines on GnRH regulation is equally recognized. Notably, norepinephrine's capacity to swiftly elevate GnRH mRNA levels has been demonstrated (He JR et al., 1993). This underscores that the stimulatory impact of norepinephrine on LH secretion is brought about via β-adrenergic receptors, whereas α-adrenergic receptors curb LH secretion. Moreover, the α-adrenergic receptor plays a role in the modulation of GnRH through steroid-mediated feedback mechanisms. (Jacobi et al., 2007).

DOPAMINE

Dopamine is an important suppressor of GnRH release (Liu X and Herbison, 2013). This shows that the D2 dopamine receptor affects GnRH release and GnRH and GnRHR gene expression in the hypothalamus. In addition, studies have shown that the D2 receptor antagonist LH pulse frequency increases, reflecting the D2 receptor's

ability to inhibit GnRH and LH pulsatility (Ciechanowska et al., 2010). Furthermore, beyond its impact on GnRH/LH, dopamine exerts a suppressive influence on prolactin secretion. The notion of a link between PCOS-reduced dopamine levels and hyperprolactinemia has been proposed (Hernández et al., 2000). Additionally, research has demonstrated the inhibitory effect of dopamine on hyperprolactinemia-related gonadotropes (Henderson et al., 2008). This suggests that diminished dopaminergic activity could contribute to heightened LH release in the context of PCOS (Kalro et al., 2001; Gómez et al., 2011). Moreover, the administration of bromocriptine, a D2 receptor agonist, has been shown to reinstate normal menstrual cycles and ovulation in PCOS-afflicted women (Kalro et al., 2001).

GABA

A significant cluster of neurons within the GnRH neural circuit comprises GABAergic cells in the medial basal hypothalamus. While GABA typically functions as the primary inhibitory neurotransmitter in the forebrain and various other brain regions, an interesting divergence occurs within GnRH neurons. This discrepancy arises from the elevated intracellular chloride concentration inherent to GnRH neurons, leading GABA to elicit stimulation in these neurons, contrary to its usual inhibitory role. This stimulation of GnRH neurons by GABA is facilitated through the GABAA receptor (DeFazio et al., **2002**). New research has revealed heightened concentrations of GABA in the cerebrospinal fluid of women affected by PCOS (Kawwass et al., 2017). Additionally, an augmentation in GABAergic postsynaptic currents impacting GnRH neurons was documented by Sullivan and

Moenter (2004). Multiple studies underscore a potential involvement of GABA neurons in the heightened activity of GnRH neurons observed in PCOS.

In conjunction with the escalation in excitatory GABAergic signaling directed at GnRH neurons, the reduction in inhibitory feedback from steroid hormones represents another contributing factor exemplified by the behavior of GnRH cells.

Apart from the shifts in GABA signaling towards GnRH neurons, there are also modifications in the regulation of GABA neurons themselves within PCOS. Notably, GABA neurons experience a decline in the expression of progesterone receptors (PR), which adds to the compromised steroid hormone feedback characteristic of PCOS. This reduction in PR expression aligns with the diminished progesterone feedback phenotype observed in certain women with PCOS (Chhabra et al., 2005). Evidence of impaired progesterone feedback in PCOS-afflicted women has been substantiated through a study revealing that women with PCOS require elevated progesterone levels to achieve the same reduction in LH as their healthy counterparts (Pastor et al., 1998). Consequently, GABA neurons could emerge as a pivotal subset, orchestrating the standard progesterone-mediated negative feedback within the modified GnRH system characteristic of a PCOS-like condition.

These two observations need not be inherently conflicting, given GABA's capability to influence various neuronal groups within the brain, with an excitatory effect on certain neurons (like GnRH neurons)

and an inhibitory impact on others. A decline in GABA levels might trigger heightened activity in afferent neurons, such as kisspeptin neurons, which in turn stimulate GnRH neurons. Nonetheless, further investigation is imperative to examine and validate this hypothesis thoroughly.

KNDy NEURONS

KISSPEPTIN

KNDy neurons constitute a cluster of neurons situated within the infundibular nucleus of the hypothalamus. They play a pivotal role in secreting three key substances: kisspeptin, neurokinin B (NKB), and dynorphin (Lehman et al., 2010; Herbison et al., 2010). The significance of KNDy neurons lies in their orchestration of the secretion of kisspeptin, the regulatory dynamic between the excitatory effects of NKB and the inhibitory effects of dynorphin, the subsequent downstream release of gonadotropins and the pulsatile release of GnRH.

Kisspeptin, synthesized from the Kiss1 gene, is a 54-amino acid protein that exerts its effects via the membrane receptor Kiss1r (Gottsch et al., 2006). Functionally, kisspeptin is a potent stimulator of GnRH neurons (Messager et al., 2005). Significantly, a positive correlation can be observed between the circulating levels of kisspeptin and the heightened levels of LH in women affected by PCOS. However, the origin of this circulating kisspeptin remains unclear (Katulski et al., 2018; Wang et al., 2019). Research findings have indicated the

involvement of kisspeptin and its receptor, Kiss1r, in regulating GnRH/LH secretion (D'Anglemont de Tassigny et al., 2007; Lapatto et al., 2007). This implies that the signaling pathway involving kisspeptin and its receptor, Kiss1r, might hold promise as a potential candidate for an affected neural mechanism in the context of PCOS.

Numerous investigations have uncovered a negative correlation between serum levels of kisspeptin and parameters such as BMI (body mass index) and indices related to insulin resistance and the free androgen index. Considerable advancements have been achieved in understanding the potential of kisspeptin as a prognostic indicator for PCOS. Kisspeptin has gained widespread recognition as a diagnostic marker, particularly in scenarios requiring differentiation between functional hypothalamic amenorrhea and PCOS. Additionally, another study has proposed that kisspeptin holds the status of an independent biomarker for PCOS. (Pérez-López et al., **2021**).

Kisspeptin indeed plays a role in the metabolic alterations observed in PCOS, a syndrome characterized by obesity, insulin resistance, and hyperlipidemia. Notably, serum levels of kisspeptin were elevated in individuals with PCOS. This increase was counteracted by a decrease in kisspeptin levels corresponding to higher BMI values, alongside an adverse correlation with glycemic and lipid profiles. Elevated serum kisspeptin levels are anticipated to contribute to an overactive hypothalamic-pituitary-gonadal axis in PCOS, leading to manifestations like menstrual irregularities, hyperandrogenemia, and hyperandrogenism. Despite these insights, Additional research is

needed to fully find out the intricate mechanisms and the precise role of kisspeptin in the pathophysiology of PCOS.

NEUROKININ B (NKB)

An array of neural and endocrine factors intricately governs GnRH secretion. Among these, NKB emerges as a key contributor (Hunjan et al., 2019). In the human body, the neuropeptide NKB is encoded by the TAC3 gene and primarily binds to the neurokinin three receptor (NK3R). Notably, NKB is pivotal as the primary regulator of GnRH secretion. In a clinical context, the impact of NKB becomes evident through an escalation in theca lutein androgen secretion coupled with a reduction in ovulation rate – a characteristic profile associated with PCOS (Osuka et al., 2017). It is worth noting that NKB also governs follicular development, gonadotropin secretion, and ovulation time in healthy women. (George et al., 2016). Elevated pituitary release of LH leads to ovulation failure and heightened ovarian testosterone production. Recent data underscores the significance of the NKB-kisspeptin-GnRH pathway in overseeing LH secretion. Specifically, individuals with compromised NKB signaling display reduced LH secretion and diminished frequency of LH pulses. Notably, studies have indicated that inhibiting NKB could offer a valuable strategy for addressing the hyperandrogenism characteristic of PCOS and central pathophysiology of excessive LH secretion.

ANDROGEN AND THE BRAIN

High circulating androgen levels are typically common in women with PCOS, and it is important to examine the PCOS pathophysiology of this type of hyperandrogenemia. Hyperandrogenism is a key feature of PCOS (Livadas et al., 2014). In hyperandrogenic PCOS, women metabolize pro-androgens present in the bloodstream into bioactive androgens through the action of enzymes like 3β-hydroxysteroid dehydrogenase (3β-HSD). This metabolic process results in the formation of different androgens, including testosterone, as well as the pro-androgens androstenedione and dehydroepiandrosterone sulfate (DHEAS) (Keefe et al., 2014; Palomba, et al., 2014). Frequently, women with PCOS exhibit an elevated LH/FSH ratio and an increased rate of LH pulses, a pattern similarly observed in PCOS models (Dumesic et al., 2015). Interestingly, while GnRH neurons oversee the secretion of LH and FSH, they lack the expression of AR (androgen receptor) (Huang et al., 1993). Instead, AR is present within the upstream neural network of the kisspeptin-neurokinin B (NKB)-dynorphin "KNDy" system located in the arcuate nucleus. This system intricately regulates GnRH secretion (Smith, 2013; Skorupskaite et al., 2014). Research has indicated the involvement of androgen receptor (AR)-mediated signaling in the modulation of the KNDy system. Additionally, certain PCOS patients exhibit an elevation in kisspeptin levels (Walters et al., 2018; Umayal and Jayakody, 2019; Katulski et al., 2018). The KNDy system is shown to be a potential therapeutic target for attenuating AR-induced neuroendocrine actions. A clinical study treating PCOS patients with a neurokinin-3 (NK3) receptor

antagonist targeted the KNDy system as its target site, reducing LH and testosterone concentrations plus the LH pulse frequency (George et al., 2016).

ANTI-MULLERIAN HORMONE (AMH)

Anti-Müllerian hormone (AMH), emanating from the ovaries, is elevated in women affected by PCOS and sustains this heightened level during pregnancy (Tata et al., 2018). Studies have indicated that external AMH administration can stimulate GnRH neurons. This suggests that elevated AMH levels might trigger the secretion of GnRH and LH (Cimino et al., 2016). The escalation in AMH levels during pregnancy results in augmented activity of GnRH neurons. Consequently, this heightened activity leads to increased LH secretion and an upswing in androgen synthesis, thus fostering a fetal environment characterized by excess androgens.

The disruption in the activity of KNDy neurons, coupled with irregular secretion of other neurohormones, could potentially trigger a breakdown in GnRH secretion. This, in turn, might prompt the heightened release of FSH and LH, thereby culminating in the development of PCOS. The insights from this study hold promise for devising novel treatment strategies for PCOS patients that target these underlying processes. Additionally, identifying distinct neurons and altered signaling factors in PCOS offers a prospect for developing prospective therapeutic interventions.

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CHAPTER XXVII

OVARIAN HYPERSTIMULATION SYNDROME ASSOCIATED WITH POLYCYSTIC OVARY SYNDROME

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Introduction

One of the highly serious side effects of assisted reproductive technologies is ovarian hyperstimulation syndrome. Ovarian hyperstimulation syndrome is at risk due to polycystic ovarian syndrome. Between 8 and 14 weeks of pregnancy, as well as in conjunction with a pituitary adenoma that produces follicle-stimulating hormone, spontaneous manifestations of the ovarian hyperstimulation syndrome are usually documented. The condition known as spontaneous ovarian hyperstimulation syndrome typically affects people who have spontaneous ovulatory cycles, particularly those who have numerous pregnancies along with hypothyroidism and polycystic ovary syndrome.

Oocytes obtained during natural and stimulated cycles are used for in vitro fertilization (IVF). Around the world, several techniques for ovarian stimulation have been used. The return of the normal cycles and "milder approaches" to ovarian stimulation in IVF have attracted significant scientific interest in the context of the development of GnRH (Gonadotropin-releasing hormone) antagonists and methods to decrease multiple births. The use of natural and "milder IVF" is patient-centered and focused at lowering treatment costs, patient discomfort, and multiple pregnancies (Nargund et al., 2007).

As an illustration, the official ART record for Italy indicates that 52 676 IVF cycles were carried out there in 2010. 9.9% (5215 cycles) of these cycles ended prior to oocyte retrieval, with 7% of IVF cycles discontinued due to poor ovarian responses, 1.5% being discontinued

due to the possibility of ovarian hyperstimulation syndrome (OHSS), and 1.7% being stopped for other reasons. In other words, up to 4500 cycles are cancelled annually in Italy alone as a result of an aberrant gonadotrophin response (La Marca & Sunkara, 2014).

Medication and ovarian stimulation are essential components of assisted reproductive technology. The adaptability of various stimulation techniques has been made possible by the accessibility of gonadotrophins and GnRH analogues. Urinary hMG and recombinant FSH (Follicle-stimulating hormone) in conjunction with GnRH agonists or antagonists are the two most often used gonadotrophin types. If not triggered on schedule, recombinant FSH-stimulated cycles seem to have a higher likelihood of an early progesterone surge in the late follicular phase. A brand-new long-acting recombinant FSH called corifollitropin alfa has just been released. It supports multiple follicular development in women receiving ovarian stimulation with GnRH antagonists for 7 days. Live birth rates between GnRH antagonist and agonist are comparable. GnRH antagonists, however, greatly lower the OHSS risk. In addition, the development of GnRH antagonists made it possible to replace hCG as a trigger for ovulation with a bolus of a GnRH agonist. With the GnRH agonist trigger, the early OHSS is completely abolished. When GnRHa is utilised in IVF/ICSI antagonist procedures to promote final oocyte maturation, a poor clinical outcome is seen due to an unrecoverable luteal phase insufficiency. As a result, it has been recommended to cryopreserve the embryos and transfer them across successive natural cycles (M Fatemi et al., 2012).

2. Ovarian hyperstimulation syndrome (OHSS)

The term "ovarian hyperstimulation syndrome" refers to a disorder in which a patient has larger ovaries following ovarian stimulation and exhibits increased vascular permeability, or leaky capillaries. Ovarian hyperstimulation syndrome (OHSS) is a potentially catastrophic iatrogenic illness of the early luteal phase and/or early pregnancy caused by an excessive ovarian stimulation response. Ascites, larger ovaries, abdominal distention and pain, and other problems sourced from ovarian vascular permeability increase are just a few of the many indications and symptoms that make up OHSS (Palomba & Caserta, 2023). Because it can result in renal failure and venous or arterial thromboembolic events, such as stroke and loss of perfusion to an extremity, in its severe form, OHSS is a disorder that poses a life-threatening risk. It has also been linked to maternal mortality. In addition, OHSS imposes a significant financial burden due to lost productivity, bed rest, hospitalisation, and intensive medical treatment of severe cases (Pellicer et al., 2019).

It is characterised by cystic growth of the ovaries, stomach pain and distention, and fluid shifting from the intravascular space to the third space. Ascites, pericardial and pleural effusions, as well as generalised edoema, may eventually occur from this condition. Although OHSS may be asymptomatic, it can occasionally result in hemoconcentration, electrolyte imbalances, hypovolemia, and coagulation problems. About 1%–5% of in vitro fertilisation cycles result in moderate-to-severe OHSS, with a frequency of up to 20% in high-risk women (Palomba & Caserta, 2023).

Age of the patient can indicate whether moderate-to-severe OHSS will occur. The likelihood of patients experiencing severe OHSS increases with age. Another patient factor that was taken into account while determining the likelihood of developing OHSS and the severity of OHSS is BMI. Women who had a BMI of less than 25 kg/m2 produce considerably less mature oocytes, needed more rFSH overall, and were at an elevated risk of having severe OHSS (Aramwit et al., 2008).

Serum AMH and AFC are two ovarian reserve markers that are particularly useful for determining OHSS risk. The antral follicle ultrasound count results and the baseline serum AMH level correspond well. According to Ocal et al. (2011), AFC (AUC = 0.74) has a moderate level of accuracy in predicting OHSS. Knowing the levels of AFC is essential for planning and managing the risks of overreaction and OHSS since AFC predicts OHSS. Elevated estradiol (E2) levels are almost always present when OHSS first manifests, and oestrogen has been suggested as a potential etiologic factor. One explanation for this association is that when estradiol levels rose, capillary permeability and the chemical mediators or precursors that promote fluid extravasation also increased, leading to the development of moderate OHSS. OHSS can be estimated by basal serum E2 levels. The quantity of recovered oocytes is a risk factor for the development of OHSS, and individuals with extremely high blood E2 levels and an excessive number of retrieved oocytes have a higher prevalence of moderate-to-severe OHSS (Mocanu et al., 2007; Sun et al., 2021).

The most severe iatrogenic side effect of ovulation induction or multifollicular formation for in vitro fertilisation is OHSS. Human chorionic gonadotropin (hCG), which is used to induce the ultimate maturation of oocyte, can either be administered exogenously or produced endogenously during pregnancy resulting in OHSS. Because the signs and symptoms of OHSS are non-specific, the clinical diagnosis has been divided into four severity levels: mild, moderate, severe, and critical. The severity of OHSS and whether or not pregnancy is present influence how it should be treated. The risk of severe OHSS after hCG administration has been reduced by a number of methods; however, their application will only lead to a decrease in the severe OHSS incidence rather than its eradication. Gonadotropin-releasing hormone (GnRH) antagonists have made it possible to utilise GnRH agonists instead of hCG for final oocyte maturation for the suppression of premature luteinizing hormone surge. As a result, severe OHSS have all but disappeared from clinical practise in assisted reproductive technologies, and the safety of ovarian stimulation has grown. The "freeze all" strategy following GnRH agonist triggering and subsequent embryo transfer is the recommended strategy to completely eradicate OHSS (Tarlatzis et al., 2019).

A modest type of OHSS may happen when ovulation is stimulated by clomiphene citrate or aromatase inhibitors, either for timed intercourse or intrauterine insemination, however moderate to severe OHSS is uncommon. The incidence of mild and severe OHSS in COS ranges from 3% to 6% and 0.1% to 2%, respectively. According to reports,

hospitalisation for OHSS can range from 0.3% to 1.1%. The OHSS incidence was alarmingly increased in the 1990s. But there has been a significant decline in this iatrogenic problem as a result of the development of risk markers and a number of prophylactic treatments, the most significant of which is the freezing of the embryos to prevent pregnancies (Pellicer et al., 2019).

OHSS is a serious, iatrogenic, somewhat unpredictable complication of assisted reproduction. Ascites, hydrothorax, pericardial effusion, hemoconcentration, enhanced capillary permeability, considerable ovarian enlargement with luteinization, and in severe cases, thromboembolic symptoms, respiratory distress, and renal failure are present. Vascular endothelial growth factors and inflammatory cytokines may be connected. The management supports correcting the fluid imbalance and maintaining renal perfusion. Serum estradiol and ultrasound serve as preventive indicators. Serum IL concentration during embryo transfer and follicular fluid interleukin IL-6 concentration at oocyte retrieval were greater in OHSS and can be used as an early predictor. Early OHSS is caused by a "excessive" preovulatory response to stimulation with increased serum estradiol (E2) levels and decreased gonadotropin requirements. Oocyte collection was higher in people with early or late OHSS than in people without OHSS. With late OHSS serum E2 and oocyte numbers could not predict risk, clinical pregnancies occurred in all cycles with late OHSS, and there were more multiple pregnancies, and late OHSS was more likely to be severe. As a result, preovulatory events and late OHSS are only marginally associated. The majority of thrombosis

instances that occur during pregnancy are late effects of OHSS. The internal jugular vein, subclavian vein, superior vena cava, and ileofemoral deep vein could all have thrombosis. Additionally, abdominal compartment syndrome could exist. Even empty follicle syndrome (after salvage), or even just using a GnRH agonist solely, do not lower the incidence of OHSS. The OHSS MR scans exhibit bilateral symmetric growth, many cystic alterations that resemble "wheelspokes," and internal haemorrhage in some cysts. Cystic neoplasm is on the differential diagnosis list. A duodenal ulcer that already exists may become perforated as a result of the stress of OHSS. There have been various alternative methods in addition to ultrasonography and careful monitoring of blood E2 levels to avoid OHSS. Human chorionic gonadotropin was deferred while daily gonadotropin-releasing hormone agonist medication was continued ("coasting") in women with Polycystic ovary syndrome (PCOS) to prevent recurrent OHSS. High doses of intramuscular progesterone were effective in preventing OHSS in high-risk women. Another approach is a single administration of gonadotropin-releasing hormone agonist to trigger ovulation while avoiding OHSS (Altchek, 2003).

3. Polycystic ovary syndrome (PCOS)

PCOS is a common gynaecological endocrinopathy disorder characterized by overexpressed luteinizing hormone triggered hyperandrogenism, chronic oligo/anovulation and polycystic ovaries morphology, with clinical manifestations described as ‘hirsutism, acne, irregular menstruation and subfertility’ (Estienne et al., 2021).

PCOS is a complex condition with many unanswered questions. The most generally used diagnostic standards for PCOS are the Rotterdam criteria, which include polycystic ovaries, physical or biochemical evidence of hyperandrogenism, and oligo/anovulation. Any two of the three will result in a diagnosis of PCOS and all associated potential repercussions after other possible complicating diseases have been eliminated out. Due to the increased risk of gynecologic malignancies, cardiovascular disease, type 2 diabetes, and infertility that comes with a PCOS diagnosis, it is crucial to make the correct diagnosis and use the right screening methods. Each PCOS sequela can be treated in a variety of ways, from lifestyle modifications to in vitro fertilisation (Waldman & Legro, 2019).

PCOS, which affects 4-6% of young people and 4-12% of adult women, may be the most prevalent endocrine condition among women of reproductive age. The connection between polycystic ovaries and hirsutism, amenorrhea, and obesity was originally noted in 1935 by Stein and Leventhal. Elevated androgen production, ovarian dysfunction, and irregular gonadotropin secretion are increasingly recognised as symptoms of PCOS. These anomalies may result in hirsutism, acne, menstrual disorders, and anovulatory infertility. Additionally, metabolic problems like insulin resistance and hyperinsulinemia are linked to PCOS. Cardiovascular disease, dyslipidemia, and Type 2 diabetes mellitus are all more common in women with PCOS. According to recent studies, paediatric conditions like early adrenarche and low birth weight are risk factors for PCOS. The symptoms of PCOS start to show up during puberty and can have

a negative impact on one's self-esteem and body image. Early detection and treatment may decrease clinical repercussions in maturity and assist regulate the physical symptoms during adolescence (Kahn & Gordon, 2008).

The 1990 NIH PCOS diagnostic standards were expanded by the 2003 Rotterdam ESHRE/ASRM (European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine). As a result, the diagnosis of PCOS in women is made when any two of the three criteria are present: Ultrasound-detected polycystic ovaries, oligo- or anovulation, biochemical or clinical evidence of hyperandrogenism, and the exclusion of other causes are the first three criteria. This diagnosis may be made after the first two to three years following menarche because anovulatory cycles are common in pubescent girls. Adolescent females frequently have polycystic ovaries, therefore it's important to be cautious when making a diagnosis of PCOS based solely on ultrasound criteria (Garfunkel et al., 2007).

4. OHSS associated with PCOS

According to Delvigne and Rozenberg (2002), the main risk factor for OHSS appears to be PCOS. PCOS, which results in an excess of antral follicles at the beginning of the cycle, causes an ovarian hyper-response to stimulation, which raises the risk of OHSS. Both early folliculogenesis and frequently a multi-follicular response after ovulation stimulation are promoted by hyperinsulinemia and hyperandrogenism, which are distinguishing characteristics of PCOS

(Dickerson et al., 2010). High insulin and/or testosterone levels may raise the risk of OHSS by causing PCOM because polycystic ovarian morphology (PCOM) is caused by hyperinsulinemia and hyperandrogenism rather than as a result of it. In vitro, luteinized granulosa cells can be stimulated to produce VEGF (vascular endothelial growth factor) by insulin and IGF-1 (insulin-like growth factor 1), although this is inadequate proof that insulin resistance is responsible directly for OHSS. OHSS is common in infertile women with PCOS, although it is also seen in infertile women without PCOS (Nikbakht et al., 2020).

Women with PCOS are more likely to get OHSS as a response to exogenous gonadotrophins at IVF treatment, which is also consistent with their increased antral follicle numbers. According to a recent meta-analysis, metformin lowers the risk of OHSS in PCOS-afflicted women undergoing ART cycle (Costello et al., 2006). Additionally, it has been proven that combining metformin with ART therapy decreases androgen levels in PCOS women and enhances the effectiveness of treatment (Tang et al., 2006).

Oligomenorrhoea is believed as a risk factor for OHSS, and according to the World Health Organisation (WHO) classification, patients in oligomenorrhoeic anovulation group II were reported to experience OHSS more frequently following induction of ovary than patients with hypogonadotrophic amenorrhoea group I (Navot et al., 1988). In most cases, patients with OHSS had hyperandrogenism in their basal hormonal profiles, and when their ovaries were examined under a microscope or by echography, they frequently had PCOS. The

frequency of OHSS was also shown to be greater in individuals who bled following a progestagen test, indicating that these patients had high oestrogen levels. In fact, PCOS revealed to be the main risk factor for OHSS even during IVF cycles. The reason could be that when stimulated using similar procedures, PCOS patients produce three times as many oocytes and follicles as normoovulatory individuals. Due to increased expression of vascular endothelial growth factor (VEGF) mRNA in the hyperthecal stroma, women with PCO may be at an elevated risk for OHSS (Delvigne & Rozenberg, 2002).

The severity of OHSS determines how it should be managed. According to available data, individuals can avoid serious sequelae by receiving prompt diagnosis and treatment. Serious OHSS need hospitalisation and urgent therapy to restore the lost intravascular volume and avoid potentially deadly consequences, including renal failure and thromboembolic events. To prevent them from moving into the critical stage, these patients should be closely watched. Due to a decrease in intra-abdominal pressure and an improvement in renal blood flow, which leads to an increase in urine production, paracentesis may be beneficial in patients with substantial ascites (Davis & Kennedy, 2006).

4. Factors associated with OHSS severity in women with PCOS undergoing IVF/ICSI

Anovulation, hyperandrogenism, and polycystic ovaries are symptoms of PCOS in patients. A common PCOS treatment is ovulation

induction. AFC, AMH, and serum E2 levels are typically increased in PCOS-afflicted women. Controlling COH in individuals with PCOS is challenging because of the increased sensitivity of polycystic ovaries to COH; as a result, COH may cause OHSS. AMH values >3.4 ng/ml, AFC >24, and estradiol values >3,500 pg/ml, according to the most recent research, are notably linked to an elevated risk of OHSS in individuals receiving fertility treatment (Pfeifer et al., 2016). OHSS risk factors include age, PCOS, high antral follicle count (AFC), low body mass index (BMI), increased anti-Muller hormone (AMH), and elevated blood estradiol (E2) concentrations. OHSS may be brought on by PCOS, a history of the condition, a high antral follicle count (AFC)a low body mass index (BMI), and young age. A history of allergies, high levels of anti-Muller hormone (AMH), large dosages of gonadotropins, and high blood E2 levels are additional risk factors (Corbett et al., 2014).

After increases in human chorionic gonadotropin (HCG) in IVF/ICSI cycles, high blood E2 levels produced by ovarian follicles may cause excessive production of vascular endothelial growth factor (VEGF) and inflammatory factors. The arterial endothelium is dilated by excessive VEGF and inflammatory substances, which may lead to a significant movement of bodily fluids into the interstitial space. PCOS is a prevalent endocrine condition that affects 5%–8% of women of reproductive age and is a major risk factor for OHSS (Mathur & Tan, 2014).

The aforementioned symptoms, however, do not provide any more clarification or indications of the severity of OHSS. Previous studies

has examined the risk factors for OHSS in the entire population receiving infertility treatment, particularly in non-polycystic ovary syndrome (NPCOS) patients, however the causes of OHSS in PCOS patients remain unknown. The most significant influence on the development of OHSS is caused by AFCs, particularly in patients with PCOS. In PCOS patients undertaking their first ovarian stimulation cycle, AFC is a distinct risk factor for OHSS. Additionally, basal serum E2 is a predictor of the severity of OHSS. The risk of OHSS in PCOS individuals undergoing IVF/ICSI can be determined by thorough ovary ultrasonography prior to therapy. The use of GnRH agonist cycles with low-dose FSH is not necessary for PCOS patients because AFC >24 is particularly related with an increased risk of OHSS, and the cutoff value is the same for NPCO patients. Instead of employing a freeze-all approach, this method will help guide cycles of fresh embryo transfer, increase the likelihood of live birth, and reduce the risk of OHSS (Sun et al., 2021).

5. Spontaneous OHSS associated with PCOS

The condition known as spontaneous ovarian hyperstimulation syndrome (sOHSS) typically affects people who have spontaneous ovulatory cycles, particularly those who have numerous pregnancies along with hypothyroidism and polycystic ovary syndrome. Women who are not pregnant rarely experience sOHSS. sOHSS is a very uncommon condition that typically strikes between weeks eight and twelve of pregnancy. Exogenous FSH therapy for OHSS results in follicle recruitment and expansion, unlike sOHSS. As a result, iatrogenic OHSS typically manifests between weeks three and five of

pregnancy. Young age, low body mass, polycystic ovarian syndrome, a sharp increase in serum estradiol levels, hypothyroidism, and a history of sOHSS are risk factors for sOHSS (Chai et al., 2020).

The majority of occurrences of OHSS are linked to the production of numerous oocytes by exogenous gonadotropins. However, among women who have had many pregnancies, hypothyroidism, polycystic ovarian syndrome, or molar pregnancies, OHSS is infrequently linked to a spontaneous ovulatory cycle. In non-pregnant women with gonadotroph pituitary adenoma and primary hypothyroidism, OHSS has only rarely been reported. On the other hand, due to excessively high serum levels of Human Chorionic Gonadotropin (HCG), spontaneous incidence of OHSS has been seen in cases of multiple pregnancies or hydatidiform moles. In addition, elevated Thyroid Stimulating Hormone (TSH) levels in hypothyroidism appear to activate the ovaries (Kim et al., 2017).

The clinical symptoms of the spontaneous form of OHSS often appear 8–14 weeks after amenorrhea and follicular recruitment and development happen later through promiscuous stimulation. Contrary to the pharmacologic variety of OHSS, which typically occurs 3-5 weeks following amenorrhea, this form of OHSS peaks at the end of the first trimester of pregnancy (Lovgren et al., 2009). Numerous incidences of spontaneous pregnancies linked to OHSS have been documented in the literature. Hypothyroidism has also been linked to familial or spontaneous OHSS with molar pregnancies. Rachad et al. (2011) provided a case of spontaneous OHSS with an invasive molar pregnancy in this context.

A pregnant woman with swollen multicystic ovaries and placentomegaly was described by Davoudian (2015). He explained how Placental Mesenchymal Dysplasia (PMD) is related to spontaneous OHSS and suggested that the most likely cause is ovarian stimulation by PMD-derived vascular endothelial growth factors.

6. Conclusions

Race, PCOS, and indicators of ovarian reserve (AMH and AFC levels), among other phenotypic traits, can all help predict a patient's chance of having OHSS. To reduce risk, specific ovarian stimulation protocols should be used. These procedures should include low-dose gonadotropin, GnRH antagonist for stopping endogenous LH surges, and GnRH agonists for ovulation start. In addition, delaying conception to a later cycle and cryopreserving oocytes and embryos are crucial steps in the prevention of OHSS. When OHSS manifests, treatment include managing symptoms and keeping an eye on vital signs, as well as performing culdocentesis of ascitic fluid replacement, intravenous liquid replacement, antithrombotic procedures, and pain management. To obtain the best results, these patients should be handled in specialised units.

The cause of PCOS, a frequent endocrinopathy, is still mostly unknown. Although the aetiology of this condition, which is characterised by unexplained persistent hyperandrogenic anovulation, is clearly variable, many women are found to have severe peripheral resistance to insulin-mediated glucose absorption and related metabolic abnormalities. Menstrual irregularities, hirsutism, infertility,

and evidence of hyperandrogenism are all symptoms of PCOS in women. Even though more carefully planned studies are required to document event risk over the course of a lifetime, they exhibit several risk factors for endometrial cancer and CVD and are at greater risk for type 2 diabetes. Treatment is frequently symptom-based.

Clinicians may focus more on the baseline serum E2 and the quantity of recovered oocytes in PCOS patients, which may help to prevent the development of OHSS. When it comes to diagnosing spontaneous ovarian hyper-stimulation syndrome (sOHSS), excluding other cystic ovarian disorders, and figuring out the underlying cause and prognosis of the condition, radiological and biochemical indicators play a crucial role. Uncovering the mysteries of this disorder depends on our ability to comprehend its pathophysiology and genetics. Treatment for sOHSS should focus on symptomatic measures such as thoracocentesis and puncture for ascites, correction of acid-base disorders, low circulating blood volume, and electrolyte imbalance, prevention of thrombosis and thrombolytic therapy and application of diuretics. Surgery should be carried out on patients who are not suitable for symptomatic treatments, particularly who have an ovarian cyst (with twisted pedicle or ruptured ovary). It is best to limit the extent of the ovary's excision as much as feasible. The ovary can be preserved if there is no ischemia necrosis of the ovary.

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CHAPTER XXVIII

POLYCYSTIC OVARY SYNDROME AND SLEEP DISORDER

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Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of reproductive age with a 10-15% prevalence in the European population (1). The combination of oligomenorrhea, infertility, hirsutism, and bilateral polycystic enlarged ovaries was described as an entity by Stein and Leventhal in 1935, and they named this syndrome after themselves for a while. The term "polycystic ovary syndrome (PCOS)" emerged in the 1960s and gradually replaced the description of Stein-Leventhal syndrome (2).

In 2003, the diagnostic criteria for PCOS were revised as a result of a workshop organized by the 'European Society of Human Reproduction and Embryology (ESHRE)' and the 'American Society for Reproductive Medicine (ASRM).' According to the Rotterdam ESHRE/ASRM criteria, at least two of the following criteria are accepted as diagnostic criteria for diagnosing PCOS (3). These criteria are as follows:

1. Oligo-anovulation,
2. Clinical or biochemical hyperandrogenism,
3. Polycystic ovaries on ultrasonography

Sleep and Women

Sleep is an essential component of normal human physiology, and sleep disorders have become common in contemporary societies in recent years. The National Sleep Foundation recommends that people aged 18-64 sleep 7-9 hours per 24 hours. Short sleep duration is defined as less than 6 hours in each 24 hours. In the US, one-third of adults complete the recommended sleep duration at night. Sleep disorders are

more common in women than men and usually coincide with fluctuations in reproductive hormones (4-6).

Circadian rhythm describes the cyclical, physiological, biochemical, and behavioral effects of the daily cycle of light and dark on living organisms. It plays an important role in the normal functioning of reproductive functions. Some hormones that have roles in reproductive function, such as thyroid stimulating hormone (TSH), luteinizing hormone (LH), and testosterone, exhibit circadian patterns under normal sleep conditions (7).

With circadian rhythm disturbance or sleep disturbance corresponding to shift work, an increase in adverse reproductive outcomes such as dysmenorrhea, menstrual irregularity, decreased time to conception, decreased conception rates, increased abortion rate, and low birth weight has been reported (8-9).

Women-specific sleep disorders are common during premenstrual dysphoria, pregnancy, postpartum depression, and transition to menopause. Some studies investigating sleep in women of reproductive age have shown that disordered sleep is associated with abortion irregularities, increased miscarriages, and adverse obstetric and perinatal outcomes (10).

While there appears to be an association between sleep disturbance and reproductive health, little is known about which sleep disturbances are associated with reproductive capacity and which specific aspects of reproductive capacity are particularly affected. Symptoms related to sleep disturbance may include sleep fragmentation, sleep continuity

disturbance, short or long sleep duration, circadian dysrhythmia, and hypoxia. Problems related to reproductive capacity may include problems with fertility, conception, implantation, pregnancy, delivery, or neonatal health (7).

Sleep in Women with Polycystic Ovary Syndrome

PCOS patients have symptoms that impair sleep quality, including difficulty falling asleep, decreased total sleep duration, decreased rapid eye movement (REM) sleep rate, decreased sleep efficiency, increased frequency of awakening, early morning awakenings, and daytime sleepiness (11). The pathophysiology of the disease and comorbid conditions have a bidirectional interaction regarding the emergence, exacerbation, and aggravation of sleep disorders.

Studies evaluating the relationship between PCOS and sleep show that the following factors have an effect on sleep patterns;

-Obstructive sleep apnea syndrome (OSA),
-Hyperinsulinemia
-Obesity
-Melatonin and
-Psychiatric comorbidity

The Effect of Sleep Apnea Syndrome and Metabolic Parameters on Sleep in Patients with PCOS

Obstructive sleep apnea (OSA) is a common disorder with important clinical consequences. This disorder is characterized by respiratory arrest accompanied by hypoxia and hypercapnia caused by repetitive

collapse of the pharyngeal airway during sleep. The clinical diagnosis of OSA is based on the presence of symptoms such as daytime sleepiness, loud snoring, witnessed respiratory interruption, and five apnea or hypopnea events per hour of sleep (Apnea-Hypopnea Index [AHI] ⩾5) detected by polysomnography. The diagnosis of OSA can also be based on an AHI ⩾15 in the absence of symptoms.

OSA is most common in middle-aged, obese men, whereas it is very rare in premenopausal women (male to female ratio, 6.5:1). After menopause, the prevalence of OSA increases significantly in women not receiving gonadal hormone replacement therapy (male to female ratio, 1.4:1). The etiology of sex differences in OSA prevalence is not fully understood. However, the role of gonadal hormones in the etiology of OSA has been blamed by assuming that androgens facilitate OSA formation and estrogens prevent OSA formation (12-13).

Among women of reproductive age in the general population, the risk of OSA has been reported to be 3%, which is lower than the risk among men of any age or older women. Numerous studies have shown an increased risk of OSA in PCOS (14).

In the study conducted in Taiwan using the National Health Database, 4595 women with PCOS and 4595 age-matched women were enrolled as the control group. OSA diagnoses of the cases were evaluated through diagnostic coding in medical records between 1998 and 2009. In the study, the prevalence of OSA was found to be significantly higher in women with PCOS ($p < 0.001$) (15).

The study by Vgontzas et al. on PCOS cases and daytime sleepiness, it was found that women with PCOS were 30 times more likely to suffer from sleep-disordered breathing than normal women. They also found that PCOS cases reported daytime sleepiness at a higher rate than women in the healthy control group (80.4% vs. 27.0%, respectively; $p < 0.001$) (16).

Obesity increases the likelihood of airway collapse by fat accumulation in the structures surrounding the upper airway. Upper body adiposity can reduce lung volume and adversely affect respiratory control. Obesity is a common feature of PCOS, and increased fat deposition in central depots has been shown even in non-obese women with PCOS. In the largest population-based study on PCOS and OSA, obesity was the only factor significantly associated with an increased risk of OSA (HR = 6.17, 95% CI: 2.43-15.69) (15). In addition, obesity increases the risk for other sleep disorders independent of the presence of OSA.

In a study by Chatterjee et al. on 50 women with PCOS, the prevalence of OSA was one in 66%. In addition, in this study, PCOS women with OSA were more obese and had higher glucose and triglyceride levels compared to PCOS women without OSA (17).

Insulin resistance and metabolic dysfunction are considered among the risk factors for OSA. Eisenberg et al. evaluated sleep parameters and risk factors for sleep disorders in infertile women with PCOS and infertile women with unexplained infertility (UI) and found that women with PCOS were more likely to have <6 hours of sleep duration, habitual snoring (snoring frequency 3-7 nights per week) and subjective daytime sleepiness than women with unexplained infertility. Measures

of insulin resistance were associated with clinical symptoms of OSA, habitual snoring, and shortened sleep duration <6 hours per night, while obesity and increased waist circumference were associated with snoring and habitual snoring (10).

Melatonin and Sleep in Patients with PCOS

Melatonin, fotoperiyodik sinyalizasyonun ritmik bilgisini çevreden organizmaya gönderen ve uyku-uyanıklık döngüsünü düzenleyen bir hormondur. Ön hipofiz bezinde farklı hormonların doğrudan/dolaylı üretimi ve salınımı için önemli bir düzenleyicidir. Bu etkisiyle melatonin, üreme süreçlerinin ve insülin salgısının düzenlenmesinde rol oynar (18).

Melatonin can be detected in follicular fluid before ovulation, which is considerably higher than serum level (19). Melatonin directly stimulates progesterone production by granulosa cells or luteal cells. It is also thought to regulate luteal function at the ovarian level (20).

Studies have shown that the levels of melatonin metabolites increased in women with PCOS, and the sleep quality of these women decreased significantly compared to women in the control group (21-22). In a study by Shabani et al., melatonin supplementation was administered for 12 weeks in PCOS patients, and as a result, it was observed that sleep quality and depression measurements improved and insulin levels decreased (23).

Psychiatric Comorbidity and PCOS Sleep Efficacy

Women with PCOS have higher rates of depression, anxiety, and sleep disorders. Sleep problems generally accompany psychiatric disorders.

Sleep and other psychiatric symptoms have mutually reinforcing and triggering effects. For example, a patient with anxiety symptoms may have sleep problems. Causes that disrupt sleep in this person may increase anxiety symptoms during the day, while increased anxiety symptoms will negatively affect nighttime sleep. Furthermore, psychiatric disorders are an additional risk factor predisposing to OSA in PCOS (24).

Improving Sleep Efficiency in PCOS Patients

Comorbid conditions should be considered when evaluating sleep-related problems in PCOS. In treating OSA and PCOS coexistence, the severity of OSA and patient compliance with treatment are important. Measures such as weight loss, reducing alcohol/sedative intake, changing sleep position, and smoking cessation are effective in reducing the severity of the disease. Devices that provide positive airway pressure prevent airway collapse by expanding the upper airway and positioning the mandible anteriorly can be used (25).

If additional psychiatric diagnosis is considered in PCOS patients, they should be referred to mental health professionals. In addition, healthy living habits and sleep hygiene can be recommended to patients.

In conclusion;

When evaluating the symptoms of sleep disorder in PCOS patients, it should be remembered that comorbid conditions (OSA, obesity, psychiatric diagnoses) interact negatively with each other and with sleep. Therefore, PCOS patients with sleep problems should be evaluated through a multidisciplinary approach.

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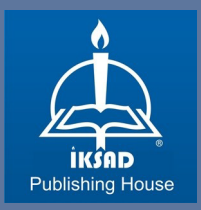

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