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MESTRADO INTEGRADO EM CIÊNCIAS FARMACÊUTICAS

EFFECTS OF ENDOCRINE DISRUPTORS ON POLYCYSTIC OVARY SYNDROME AND NEW THERAPEUTIC APPROACHES

Trabalho submetido por
Adèle Lemogne Robert
para a obtenção do grau de Mestre em Ciências Farmacêuticas

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Trabalho orientado por
Professora Doutora Catarina Jota Baptista

e coorientado por
Professora Doutora Edite Oliveira-Torres

julho de 2025

Dedicatória

« Dans la vie rien est à craindre, tout est à comprendre. C'est maintenant le moment de comprendre davantage, afin de craindre moins. »

Marie Curie

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Resumo

A síndrome dos ovários poliquísticos (PCOS) é uma doença endócrina que afecta cerca de 10% das mulheres em todo o mundo. Os sinais clínicos e as alterações associadas incluem hiperandrogenismo, ciclos menstruais irregulares, infertilidade, resistência à insulina associada a um risco de *diabetes mellitus* tipo 2, doença cardiovascular, doença metabólica, ansiedade e depressão. No entanto, as causas e a patologia ainda são pouco conhecidas. Ainda não foi descrito nenhum tratamento curativo eficaz para esta síndrome, pelo que as abordagens terapêuticas se baseiam na gestão dos sinais clínicos.

Alguns estudos científicos evidenciaram a toxicidade de certos desreguladores endócrinos (EDCs), como o bisfenol A e os ftalatos, mostrando os seus efeitos nas funções hormonais e ováricas associadas a perturbações da infertilidade como a PCOS. Estudos demonstraram que o bisfenol está frequentemente presente no plasma, na urina e no fluido folicular de mulheres com PCOS.

As terapias tradicionais, como as pílulas contraceptivas ou a metformina, estão a ser cada vez mais complementadas com outras abordagens terapêuticas, como os agonistas dos receptores GLP-1, as citocinas e os inibidores SGLT2.

Estudos recentes têm discutido algumas opções terapêuticas que têm por objetivo eliminar ou neutralizar os EDCs, bem como a terapia genética, a terapia epigenética, as nanotecnologias e os sequestradores enzimáticos de EDCs, para reduzir a toxicidade destes desreguladores.

Uma melhor compreensão do impacto dos EDCs e de outras causas na PCOS permitirá o desenvolvimento de novas abordagens terapêuticas para tratar estes doentes e reduzir os sinais clínicos da PCOS. Por conseguinte, o objetivo deste trabalho é apresentar uma revisão atualizada da PCOS, centrando-se nos efeitos dos EDCs na sua etiologia e em novas abordagens terapêuticas para este síndrome.

Palavras-chave: síndrome dos ovários poliquísticos (PCOS); desreguladores endócrinos (EDCs); Bisfenol A; toxicidade; hiperandrogenismo; infertilidade; novas abordagens terapêuticas

Abstract

Polycystic ovary syndrome (PCOS) is an endocrine disease affecting around 10% of women worldwide. Clinical signs and associated alterations include hyperandrogenism, irregular menstrual cycles, infertility, insulin resistance associated with a risk of type 2 *diabetes mellitus*, cardiovascular disease, metabolic disease, anxiety and depression. However, the causes and pathology are still poorly understood. No effective curative treatment for this syndrome has yet been described, so therapeutic approaches are based on managing clinical signs.

Some scientific studies highlight the toxicity of certain endocrine disruptors (EDCs), such as bisphenol A and phthalates, showing their effects on hormonal and ovarian functions associated with infertility disorders such as PCOS. Studies have shown that bisphenol is frequently present in the plasma, urine and follicular fluid of women with PCOS.

Traditional terapies, such as contraceptive pills and metformin, are increasingly supplemented by other therapeutic approaches such as GLP-1 receptor agonist, Cytokine, SGLT2 inhibitors.

Recent studies have been discussing some therapeutic options that aim to eliminate or neutralize EDCs, as well as gene therapy, epigenetic therapy, nanotechnologies and EDC-scavenging enzymes, to reduce the toxicity of these disruptors.

A better understanding of the impact of EDCs and other causes on PCOS would enable the development of new therapeutic approaches to treat these patients and reduce the clinical signs of PCOS. Therefore, the aim of this work is to provide an updated review of PCOS, focusing on the effects of EDCs on its etiology and on new therapeutic approaches to this syndrome.

Keywords: Polycystic ovary syndrome (PCOS); endocrine disruptors (EDCs); Bisphenol A; toxicity; hyperandrogenism; infertility; new therapeutic approaches

Résumé

Le syndrome des ovaires polykystiques (PCOS) est une maladie endocrinienne qui touche environ 10 % des femmes dans le monde. Les signes cliniques et les altérations associées comprennent l'hyperandrogénie, des cycles menstruels irréguliers, l'infertilité, la résistance à l'insuline associée à un risque de diabète sucré de type 2, les maladies cardiovasculaires, les maladies métaboliques, l'anxiété et la dépression. Cependant, les causes et la pathologie sont encore mal comprises. Aucun traitement curatif efficace de ce syndrome n'a encore été décrit, les approches thérapeutiques sont donc basées sur la gestion des signes cliniques.

Certaines études scientifiques mettent en évidence la toxicité de certains perturbateurs endocriniens (EDCs), tels que le bisphénol A et les phtalates, en montrant leurs effets sur les fonctions hormonales et ovariennes associées à des troubles de l'infertilité tels que le PCOS. Des études ont montré que le bisphénol est fréquemment présent dans le plasma, l'urine et le liquide folliculaire des femmes atteintes du PCOS.

Les thérapies traditionnelles comme les pilules contraceptives, les antioxydants et la metformine sont de plus en plus supplémentées par des approches thérapeutiques alternatives telles que le GLP-1 récepteur agoniste, la Cytokine, SGLT2 inhibiteurs.

De récentes études ont parlé de thérapies visant à éliminer ou neutraliser les EDCs, il existe aussi des thérapies géniques, thérapies épigénétiques, nanotechnologies et enzymes piégeuses de EDCs, pour réduire la toxicité de ces perturbateurs.

Une meilleure compréhension de l'impact des EDCs et d'autres causes sur le PCOS permettrait de développer de nouvelles approches thérapeutiques pour traiter ces patientes et réduire les signes cliniques du PCOS. Par conséquent, l'objectif de ce travail est de fournir une revue actualisée du PCOS, en se concentrant sur les effets des EDCs sur son étiologie et sur les nouvelles approches thérapeutiques de ce syndrome.

Keywords: syndrome des ovaires polykystiques (PCOS); perturbateurs endocriniens (EDCs); Bisphénol A; toxicité; hyperandrogénie; infertilité; nouvelles approches thérapeutiques

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List of Abbreviations and Acronyms

AE-PCOS - Androgen Excess-Polycystic Ovary Syndrome Society

AI - Artificial intelligence

AMPK - Adenosine monophosphate activated protein kinase

AMH - Anti-Müllerian Hormone

BFRs - Brominated Flame Retardants

BPA - Bisphenol A

BPF - Bisphenol F

BPS - Bisphenol S

BMI - Body Mass Index

COCs - Combined Oral Contraceptives

CPA - Cyproterone acetate

CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats

DDT - Dichlorodiphenyltrichloroethane

DEHP - Di(2-ethylhexyl) phthalate

DENNDA - DENN Domain Containing 1A

DHT -Dihydrotestosterone

DNMT - DNA Methyltransferase

EDCs - Endocrine Disruptive Chemicals

EE - Ethinyl estradiol

EPA - Environmental Protection Agency

ERα - Estrogen Receptor Alpha

FSH -Follicle-Stimulating Hormone

GLP1-RA - Glucagon-like Peptide-1-Receptor Agonists

GRH - Gonadotropin-Releasing Hormone

HDAC - Histone Deacetylase

HDL - High-Density Lipoprotein

HPG Axis - Hypothalamic-Pituitary-Gonadal Axis

IL-6 - Interleukin-6

INSR - Insulin Receptor

IUD - Intra Uterine Devices

IVF - In Vitro Fertilization

LAHR - Laser-Assisted Hair Removal

LDL - Low-Density Lipoprotein

LH - Luteinizing Hormone

LHCGR - Luteinizing Hormone/Choriogonadotropin Receptor

miRNAs - MicroRNAs

NAFLD - Non-Alcoholic Fatty Liver Disease

NASH - Non-Alcoholic Steato Hepatitis

NIH - National Institutes of Health

PAMH - Prenatal AMH exposure

PCOS - Polycystic Ovary Syndrome

PFAS - Perfluoroalkyl and Polyfluoroalkyl Substances

POCs - Progestin-only contraceptives

PREVED - Pregnancy prevention endocrine disruptors

SGLT2 - Sodium-Glucose Cotransporter-2

SHBG - Sex Hormone Binding Globulin

THADA - Thyroid Adenoma Associated

TNFα - Tumor Necrosis Factor Alpha

VLCKD - Very Low-Calorie Ketogenic Diet

WHO - World Health Organization

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disease. It affects between 6% and 13% of women of childbearing age, making it a public health challenge, even though this percentage may vary according to the more or less strict criteria used for diagnosis (World Health Organization, 2025). This hormonal and metabolic disease is mainly characterized as an excess of androgens, ovulation difficulties, and ovarian morphological alterations. Moreover, it is often associated with insulin resistance, increased risk of type 2 diabetes. Currently, there is not an effective and definitive cure for PCOS. The existing treatments are based on minimizing the clinical signs of this syndrome.

Since PCOS affects many women, pharmacists are likely to frequently encounter patients with this syndrome in their daily practice. Moreover, PCOS often requires a combination of treatments, including medications, nutritional supplements and lifestyle changes (Myriam Gorzkowski, 2020). Thus, pharmacists play an essential role, helping with the management of multiple treatments and preventing potential drug interactions. A good understanding of PCOS enables pharmacists to provide personalized, up-to-date information, contributing to better patient care.

Additionally, PCOS is a chronic condition that requires long-term follow-up (Abraham Thomas, 2017). Therefore, pharmacists can play an important role in this follow-up, helping patients to adhere to their treatments and monitoring the onset of side effects or complications.

The pharmacist is accessible and plays the role of first point of contact, as well as providing follow-up and referral to the appropriate healthcare professional, since this syndrome affects affected women in many ways. General practitioners provide comprehensive follow-up and can also refer patients to specialists (GENESIS, n.d.; Lancet Regional Health – Europe, 2022).

I. Polycystic ovary syndrome (PCOS)

A. Pathophysiology, clinical signs and diagnostic criteria

A syndrome is a set of symptoms and clinical signs that appear together and characterize a specific medical condition or disorder (University of Utah Health, 2017). PCOS syndrome is an incurable endocrine and reproductive disease, whose first symptoms generally begin in adolescence, although they may become more obvious or evolve over the years and be diagnosed later in life. The biological and hormonal mechanisms involved in the development of PCOS include hyperandrogenism, insulin resistance and dysfunction of the hypothalamic-pituitary axis. These mechanisms and their interactions form the complex pathophysiology of PCOS (Dong & Rees, 2023).

Regarding hyperandrogenism, ovaries produce abnormally high levels of androgens, mainly testosterone. Insulin resistance leads to elevated blood insulin levels, and the dysfunction of the hypothalamo-hypophyseal axis functions is associated to abnormal levels of hormones, as higher levels of luteinizing hormone (LH) than follicle-stimulating hormone (FSH), which leads to a disruption in women's hormonal and menstrual cycles (World Health Organization, 2025).

Other associated pathophysiological mechanisms include disturbed follicular development. In PCOS, follicles fail to mature properly, resulting in anovulation and an accumulation of small and undeveloped follicles, due to the elevated levels of LH and reduced levels of FSH, which disrupts normal ovarian function (Silva et al., 2023). PCOS is also associated with persistent chronic low-grade inflammation, marked by increased cytokines, which can also lead to hormonal and metabolic disturbances and clinical signs, such as chronic fatigue, joint pain, digestive problems and inflammatory acne. The pathophysiology of PCOS is also associated with oxidative stress. In fact, excessive free radicals and deficient antioxidant defenses contribute to oxidative stress, and are associated with insulin resistance, hyperandrogenism, metabolic and cardiovascular complications. Vitamin D, known for its antioxidant and anti-inflammatory properties, is often

deficient in women with the syndrome. An elevated insulin level caused by the syndrome can decrease the activity of enzymes that are responsible for converting inactive vitamin D into its active form, thus leading to vitamin D deficiency (Han et al., 2024). The supplementation with vitamin D may help counteract effects of the syndrome. Women with PCOS often have dyslipidemia characterized with high triglyceride levels, high Low-Density Lipoprotein (LDL) cholesterol and low High-Density Lipoprotein (HDL) cholesterol, increasing their vulnerability to cardiovascular disease. These lipid imbalances are also often linked to insulin resistance and obesity (Prapas N et al., 2009).

Table 1- Summary of pathophysiology of PCOS. Source : original.

Pathophysiology	Clinical Signs	Associated Diseases
Hyperandrogenism	Hirsutism, acne, androgenetic alopecia, oily skin	Endometrial hyperplasia and endometrial cancer
Dysfunction of the hypothalamic-pituitary axis	Menstrual disorders (oligomenorrhea, amenorrhea), infertility	Infertility
Insulin resistance and hyperinsulinemia	Weight gain	Type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease
Follicular development alteration	Menstrual disorders, difficulty conceiving	Infertility
Chronic low-grade inflammation	Inflammatory acne, joint pain, chronic fatigue, digestive problems	Increased risk of cardiovascular diseases

Oxidative stress	No directly observable clinical signs	insulin resistance, hyperandrogenism, metabolic and cardiovascular complications
Dyslipidemia	No directly observable clinical signs	Cardiovascular diseases, atherosclerosis

As mentioned above, PCOS is normally associated with hyperandrogenism, due to neuroendocrine dysfunction, and metabolic imbalance. Hyperandrogenism is characterized by the presence of oxygenated 11-androgens. Unlike testosterone and dihydrotestosterone (DHT), which are already active, these oxygenated androgens circulate in precursor form before being converted to functional androgens in certain tissues. These oxygenated 11-androgens include 11-ketotestosterone, which binds to androgen receptors with a potency like that of testosterone. This androgens' class is particularly present PCOS patients and increases the risk of metabolic disorders, particularly insulin resistance and obesity. Oxygenated 11-androgens act as passive precursors in peripheral tissues, and then become active androgens, like testosterone. The overproduction of androgens that characterize PCOS directly interferes with the functioning of the hypothalamic-pituitary-ovarian axis, with an elevated production of the gonadotropin-releasing hormone (GRH), resulting in neuroendocrine dysfunction. This over-secretion leads to constant higher level of LH than FSH, and consequently an accumulation of immature follicles in the ovary, resulting in anovulation. The rise in LH levels induces increases testosterone production by ovarian thecal cells, leading to the hormonal imbalances of PCOS, and to disturbances in cortisol metabolism. This cascade of reactions promotes insulin resistance and, consequently, the development of type 2 diabetes. In addition, this combination promotes greater sympathetic nerve activity, linked to increased risk of cardiovascular complications, oxidative stress, hormone-dependent cancers and psychiatric disorders, as described in subchapter I-C (Dong & Rees, 2023; Dumesic et al., 2015).

Regarding diagnosis, there are three published guidelines and criteria for diagnosing PCOS: the Rotterdam Criteria (2003), the Androgen Excess-PCOS Society (2006) (AE-PCOS Society

Criteria), and the National Institutes of Health Criteria (1990) (NIH Criteria). Figure 1 illustrates and summarizes these three criteria (Choudhari et al., 2024).

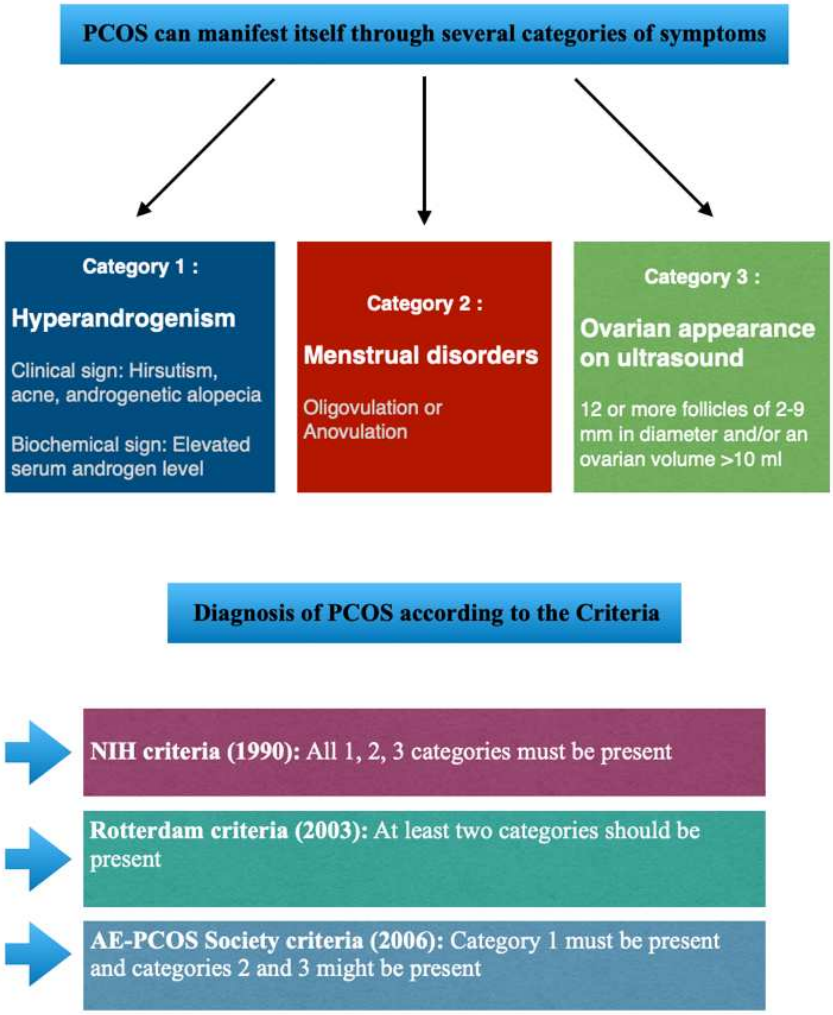

Figure 1 - Diagram summarizing the diagnostic criteria for PCOS. Source: Original, based on Choudhari et al., (2024).

To provide a sustained diagnose of PCOS, the Rotterdam Criteria (2003) requires two of the following three abnormalities: clinical or biological hyperandrogenism, ovulatory dysfunction (oligo/anovulation), and polycystic ovarian morphology on ultrasound examination. Clinical

hyperandrogenism is often presented by hirsutism, acne and/or androgenetic alopecia. Biological hyperandrogenism is characterized by elevated androgens in the blood (Tarlatzis (Gr), 2003).

According to the Rotterdam criteria, polycystic ovarian morphology on ultrasound is validated by the presence of twelve or more follicles in each ovary measuring 2 to 9 mm in diameter and/or an increase in ovarian volume (more than 10 ml) in at least one ovary (Figure 2). When diagnosing PCOS on medical imaging, especially with older equipment, some forms may be confused with cysts. For a long time, small and immature follicles were frequently confused with ovarian cysts, leading to the use of the term “polycystic ovaries”. Nowadays, with better ultrasound equipment the description of this alteration is more accurate. Ovarian follicles contain eggs destined to be released at ovulation. However, a hormonal imbalance can disrupt this release, preventing full development. The follicles then remain at an immature stage and accumulate in the ovaries (Zeng et al., 2022).

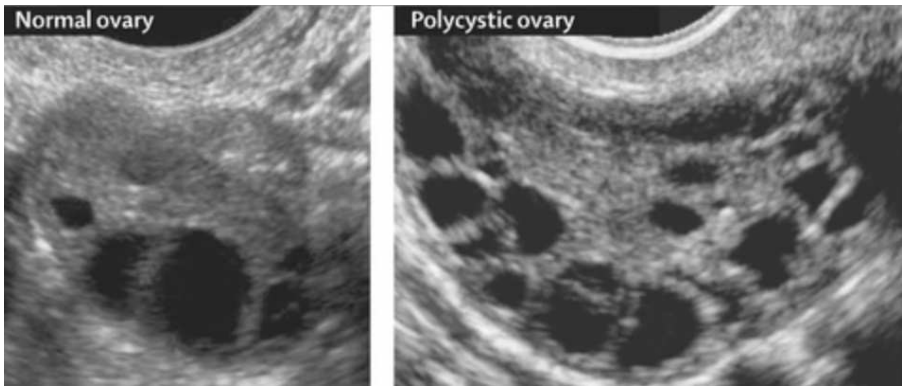

Figure 2 - Comparative ultrasound of an ovary without PCOS and with PCOS. Source: Alice Monney, (2022).

The AE-PCOS Society (2006) criteria focus on hyperandrogenism and ovulatory disorders, while considering the morphological appearance of the ovaries on ultrasound (Azziz et al., 2009).

In contrast, the NIH criteria (1990) are stricter, only focusing on hyperandrogenism and dysovulation. In other words, hyperandrogenism and menstrual disorders are mandatory for the diagnosis and classification of PCOS, without including the morphological appearance of the ovaries on ultrasound (Tarlatzis (Gr), 2003).

The choice of criteria depends on the clinical context and therapeutic objectives, but the heterogeneity of the clinical manifestations of this syndrome requires a personalized approach and monitoring for each patient. The prevalence of the syndrome is 6-10% when the diagnostic criteria are defined by the NIH, compared with a prevalence closer to 12-21% with the Rotterdam and AE-PCOS Society criteria. A higher prevalence is considered when the criteria applied for the diagnosis is more flexible, as what happens when clinicians use the Rotterdam criteria, instead of the NIH criteria (Dong & Rees, 2023; Dumesic et al., 2015).

Hirsutism takes the form of excessive hair growth on male areas and can be seen on typically masculine areas such as the chin, chest and back. androgenetic alopecia is visible hair loss on the crown of the head, caused by hormones. Acne due to PCOS appears via sebum hypersecretion under the effect of androgens. Hirsutism, acne and alopecia due to hyperandrogenism are caused by higher testosterone production, often aggravated by higher conversion to DHT. Studies have shown that conversion by the enzyme 5-alpha reductase of testosterone into DHT promotes the transformation of fine hair into thicker, more visible hair. This induces excessive hair growth in a male model of women with PCOS. Regarding acne, DHT stimulates the sebaceous glands, increasing sebum production and thus contributing to the appearance of acne. Concerning alopecia, DHT reduces the size and growth of hair follicles in the scalp area, due to activity of the enzyme 5-alpha reductase (Azziz et al., 2006; Dumesic et al., 2015).

PCOS patients often a clinical sign of menstrual disorders, such as oligomenorrhea (irregular or spaced menstrual cycles) or amenorrhea (absence of periods), which are also related to anovulation or oligo-anovulation (insufficient ovulation). The AE-PCOS Society (2024) reported that around 85% of women with PCOS have ovulatory problems, with only 50% having ovulatory cycles. In contrast, according to the Dumesic et al., 2015, 16% of a total of 316 women diagnosed with PCOS (according to NIH criteria) experienced oligo-anovulation, despite usually having regular menstrual cycles. Anovulation can be detected by measuring serum progesterone levels during the luteal phase of the cycle. A progesterone level below 3-4 ng/mL indicates an oligo-anovulatory cycle. Since chronic anovulation can lead to infertility in women with PCOS, it is important to detect these cases of anovulation early enough in adolescence to improve the condition of these young women (Dumesic et al., 2015). However, it is not easy to detect anovulation during the first menstrual period. In the case of adolescents, irregular cycles may predict the risk of long-term

oligomenorrhea, but this does not necessarily involve a diagnosis of PCOS, since irregular cycles are frequent and normal in the first years after menarche. A study by van Hooff et al., 2004 sheds light on this subject, comparing two groups of teenage girls with irregular menstrual cycles; one group whose average menstrual cycle length was 35 to 41 days, and other group whose cycles lasted 22 to 34 days. Four years later, the study found that 10% of women with shorter cycles (22 to 34 days) were affected by oligomenorrhea, compared with 50% of women with longer cycles (35 to 41 days). Longer menstrual cycles are therefore markers of possible long-term development of oligomenorrhea in women. Therefore, when diagnosing PCOS, it is necessary to consider age-related variations in the naturalness of menstrual cycles. It's also important to consider that apparently regular cycles are not always signs of ovulatory cycles (Azziz et al., 2006; Dumesic et al., 2015).

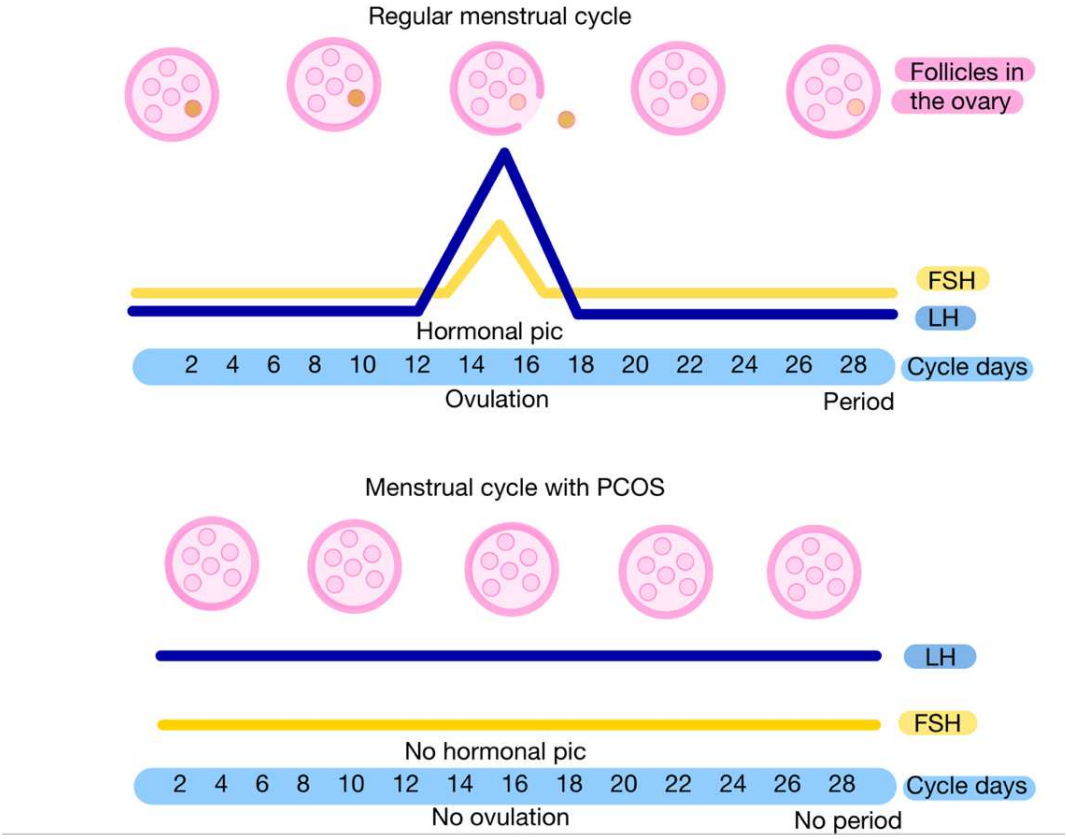

Figure 3 – Menstrual cycle in PCOS. Source: Original based on Hôpitaux Universitaire de Genève, (n.d).

PCOS has significant long-term mental consequences for the women. According to the WHO, most women with PCOS experience psychological problems such as anxiety, depression and consider themselves as having a poor body image. In fact, women affected by PCOS are around three times more likely to suffer from depressive symptoms than women without the syndrome. Several factors explain this psychological fragility, namely the psychological and social challenge that physical symptoms of PCOS, such as infertility, hirsutism, androgenetic alopecia, acne, obesity and diabetes, may represent. All these directly affect self-esteem and generate feelings of anxiety and a social stigma.

Additionally, the hormonal imbalances of PCOS, which affect the neurochemical balance, may also contribute to mood disorders. That's why it's advisable to listen to patients to prevent and manage these long-term mental consequences and consider psychological support, and not just treat the physical symptoms of PCOS (Alur-Gupta et al., 2019; Y. Li et al., 2024; WHO, 2025).

Imbalances in the gut microbiota, particularly high levels of *Bacteroides vulgatus*, have also been recently reported as associated with PCOS. In these studies, the fecal microbiota of PCOS patients was introduced into mice. For instance, Dong & Rees (2023) found that "*oral gavage of wild-type mice with faecal microbiota from individuals with polycystic ovary syndrome (…) caused insulin resistance, changes in bile acid metabolism, reduced secretion of interleukin 22, and disrupted oestrous cycle and ovarian morphology*." Thus, this imbalances in the gut microbiota could induce systemic inflammation, insulin resistance and hormonal imbalances, contributing to the metabolic and endocrine symptoms in PCOS patients (Dong & Rees, 2023; Qi et al., 2019).

As mentioned, women with PCOS often present metabolic complications such as insulin resistance, accompanied by compensatory hyperinsulinemia, putting them at increased risk of developing impaired glucose tolerance and type 2 *Diabetes mellitus* (Dumesic et al., 2015). Although abdominal obesity exacerbates insulin resistance, studies show that thin women with PCOS may have similar resistance to obese women, indicating the importance of genetic factors in this syndrome. Even though insulin resistance in women with PCOS can occur independently of body weight, due to hormonal and genetic factors, it is usually aggravated by obesity. Insulin resistance affects 70% of women with PCOS, regardless their body condition. In women without PCOS, the prevalence of type 2 diabetes is 0.7%. In comparison, the prevalence of type 2 diabetes in patients with PCOS ranges between 7.5% and 10% (Scicchitano et al., 2012).

It is common to observe dyslipidemia in women with PCOS, with high triglyceride levels and low HDL cholesterol. This dyslipidemia, combined with insulin resistance, significantly increases cardiovascular risk in these women (Dong & Rees, 2023). The whole relationship between PCOS and cardiovascular risk can be explained by several factors, such as insulin resistance, the prevalence of type 2 diabetes, and elevated plasma levels of the amino acid homocysteine. Homocysteine is a cardiovascular risk factor and can cause endothelial cell damage, muscle cell proliferation, increased inflammatory cytokine activity and atherogenesis. Atherogenesis refers to the process by which deposits of fats, cholesterol and other substances form atheromatous plaques in arteries, causing blood vessels to narrow and harden. Homocysteine can damage the inner lining of blood vessels, disrupting their function and facilitating clot formation. High levels of homocysteine damage the smooth muscle cells of blood vessels, leading to their proliferation and a reduction in vessel flexibility, reducing their ability to dilate and contract normally. An increase in inflammatory cytokine activity means that inflammation in the body is intensified, promoting immune response and potentially contributing to vascular disease (Galera et al., n.d.; Prapas N. et al., 2009; Scicchitano et al., 2012).

These findings highlight the importance of cardiovascular risk assessment and management in women with PCOS, independently to their body mass index (BMI). Scicchitano et al., (2012) suggested interventions to reduce homocysteine levels, such as folic acid therapy, which is involved in homocysteine catabolism. In fact, the AE-PCOS Society, (2024) recommended that women with PCOS have their blood pressure measured at every visit for the prevention of cardiovascular disease.

Non-alcoholic fatty liver disease (NAFLD) results from an abnormal accumulation of lipids in the liver, making it more vulnerable to damage and inflammation. It can evolve into Non-Alcoholic SteatoHepatitis (NASH), characterized by hepatocyte damage and apoptosis. If untreated, persistent inflammation can lead to cirrhosis. Insulin resistance is present in up to 80% of NAFLD cases, since it leads to an increased flow of free fatty acids to the liver, causing hepatic steatosis (Kelley et al., 2014). A study by Asfari et al. (2020) has demonstrated the association of NAFLD and PCOS, indicating that PCOS women are four times more likely to develop NAFLD than women without PCOS. The Karoli et al. (2013) explained this association, referring that insulin resistance, obesity, dyslipidemia and hyperandrogenism are associated with PCOS and may

contribute to the development of NAFLD by promoting hepatic fat accumulation, increasing lipogenesis, reducing lipid oxidation, and inducing chronic inflammation. Understanding this strong association between PCOS and NAFLD may help improve clinical management and prevent long-term complications in women with PCOS, such as cirrhosis.

Endometrial cancer is also a possible long-term consequence of PCOS. Some symptoms and conditions associated with PCOS (as obesity, prolonged exposure to unopposed estrogens, infertility, hypertension and *Diabetes mellitus*) predispose, in the long term, to the development of endometrial, ovarian and breast cancers. Although there is yet no substantiated evidence for this correlation, an association has been observed between PCOS and a family history of breast cancer (Daniilidis A. & Dinas K., 2009).

The current working context for pharmacists concerning PCOS is marked by a growing awareness of the prevalence and impact of this condition on women's health. Moreover, the complexity of PCOS, with its multiple clinical manifestations and long-term health implications, requires a multidisciplinary and personalized treatment approach for each woman (Teede et al. 2023). Because of the high prevalence of the syndrome, the complexity of treatment, the need for quality guidance and education of women about their syndrome, the long-term follow-up of this chronic condition that evolves throughout the patient's life, and the advances in research on the subject, it is crucial for a pharmacist to know and study PCOS. Specialists who can help monitor women's symptoms and can be consulted are listed in Figure 4.

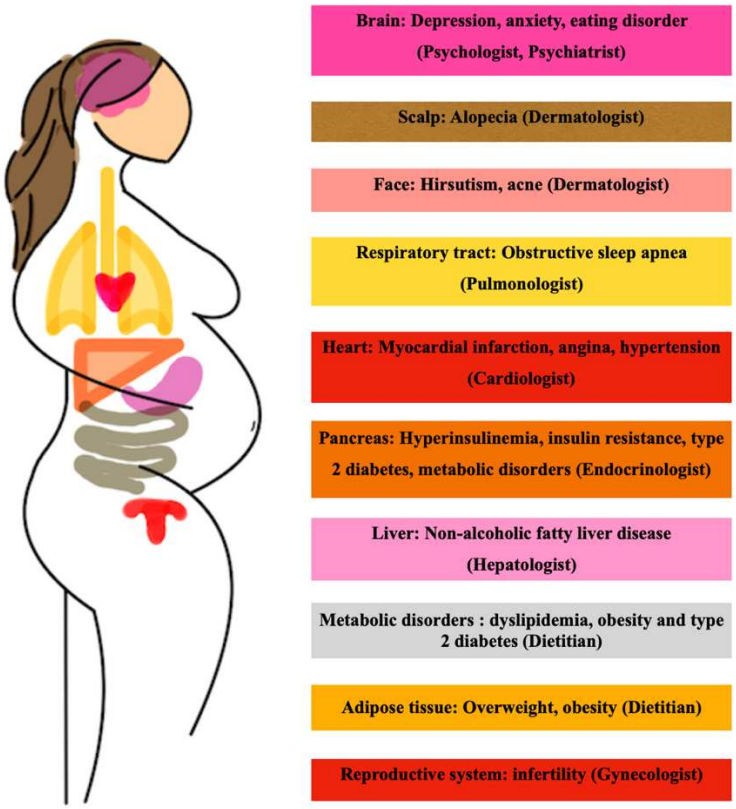

Figure 4 - Multidisciplinary Approach to Management of PCOS. Source: original based on Dason et al., (2024).

PCOS research is constantly evolving, with new therapeutic approaches emerging. Pharmacists' in-depth knowledge of PCOS is essential to improve the quality of care, optimize treatment management and contribute to a better quality of life for women with this syndrome.

B. Genetic and environmental factors: exploring possible predisposing factors and causes.

The pathophysiology of PCOS is commonly associated with genetic predisposition, such as epigenetic alterations that modify gene expression. These alterations involve changes in methylation, influence key genes and can be transmitted over several generations. Factors such as

the intrauterine environment, anti-Müllerian hormone (AMH) and lifestyle during pregnancy play a major role. This is known as via fetal programming (incidents that disrupt the fetus development and increase the risk of chronic diseases in adulthood), and explains the high hereditary component of the syndrome, with 60-70% of daughters born to mothers with PCOS developing symptoms (Mimouni & Giacobini, 2024).

As stated by Dumesic et al., (2020) "*a recent longitudinal study of daughters born to women with PCOS and followed from infancy to post-menarche, [suggested] a 62% transmission of PCOS phenotype."* In addition, studies on twins estimate that PCOS predisposition is hereditary in 71% of monozygotic twins and in 38% heterozygotic twins (Dumesic et al., 2020). Similarly, sisters with PCOS have an increased frequency of hormonal alterations, such as elevated androgen levels, and 22% of sisters of women with PCOS meet the diagnostic criteria for PCOS, showing the importance of the genetic factor (Dumesic et al., 2015).

However, genetic research has not fully explained this inheritance yet. There is still a lot of research to be done to identify the genes linked to PCOS. Some of which influence reproductive function (such as FSH Receptor, Luteinizing Hormone/Choriogonadotropin Receptor (LHCGR), AMH, and DENN Domain Containing 1A (DENNDA), and others affect metabolism (such as Insulin Receptor (INSR), and Thyroid Adenoma Associated (THADA). These genes do not act in isolation, but interact with each other and with external factors, making the genetic origin of PCOS particularly complex. The diagram below (Figure 5) shows that exposure to EDCs during pregnancy can interfere with the development of the fetus (F1 generation) by modifying the hormonal environment, which is essential to its growth and maturation. Furthermore, these substances can induce epigenetic modifications in fetal DNA, which can be passed on to subsequent generations (F2 and F3). These intergenerational effects suggest that exposure to EDCs may contribute to the predisposition to PCOS and other hormonal and metabolic disorders over several generations (A. Z. Rutkowska & Diamanti-Kandarakis, 2016).

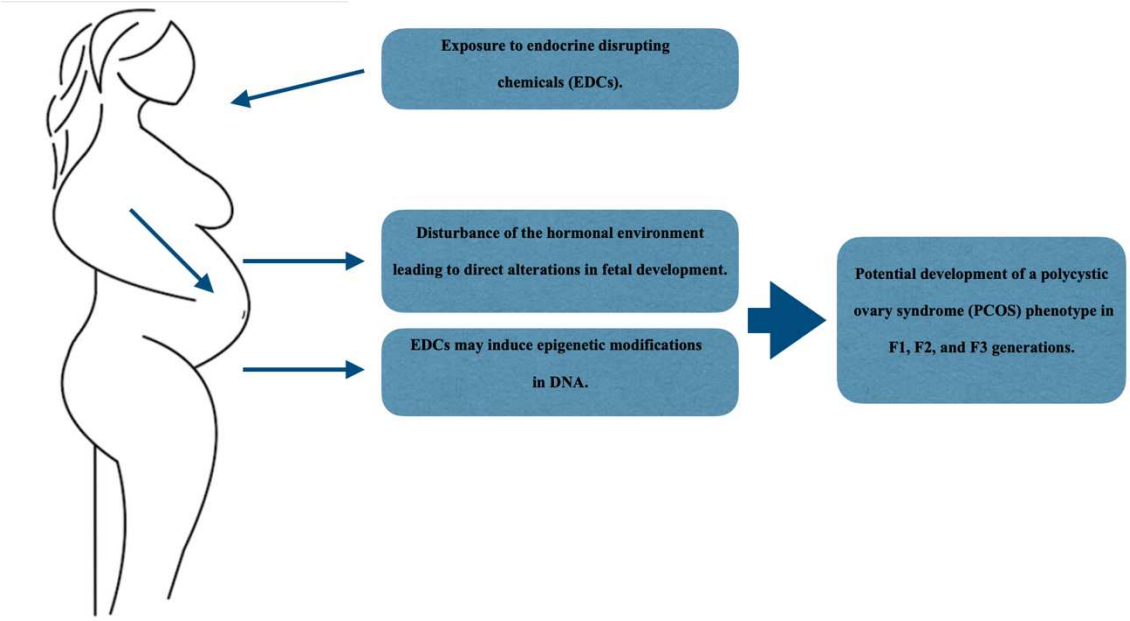

Figure 5 - EDCs and Epigenetic Inheritance. Source: original based on A. Z. Rutkowska & Diamanti-Kandarakis, (2016).

An intrauterine environment with high levels of AMH can disrupt fetal development. These imbalances influence the hypothalamic-pituitary-gonadal axis (HPG) and cause hormonal and metabolic abnormalities in the baby, characteristic of PCOS, such as hyperandrogenism, oligo-anovulation, fertility disorders and insulin resistance.

Research on mice called PAMH (Prenatal AMH exposure) revealed significant metabolic disturbances in the PAMH lineage over subsequent generations, compared with control groups. These disturbances affected body composition, influenced hyperglycemia, insulin resistance and/or fat mass gain, which also suggests the importance of a balanced hormonal environment during pregnancy to prevent long-term consequences on the reproductive and metabolic health of the baby (Mimouni & Giacobini, 2024).

Exposure to EDCs is increasingly being studied as an environmental factor for predisposition to PCOS. Some of these chemicals, such as bisphenol A (BPA), phthalates and pesticides, are widely present in the environment and can interfere with the hormonal system in a few of ways (Silva et

al., 2023). Human exposure can occur via a variety of routes, including ingestion via food, inhalation or dermal absorption, raising concerns about their effects on health (Darbre, 2017).

Studies suggest that phthalates can alter the HPG axis. Exposure can *"disrupt follicle growth pattern, increase oxidative stress and cause follicle death"* (Silva et al., 2023). Moreover, in women, high levels of urinary phthalates were correlated with "*decreased rates of pregnancy, increased rates of miscarriages, pregnancy complications as well as a diminished ovarian reserve*" (Silva et al., 2023), reinforcing the idea of a link between exposure to EDCs (such as phthalate) and ovarian diseases.

On the other hand, frequent exposure to BPA can disrupt the HPG axis. Kisspeptin is a neuropeptide that modifies the frequency and intensity of signals transmitted to the hypothalamus to release GRH. When kisspeptin is disrupted, the release of GRH also disrupts, reducing the stimulation and release of gonadotropins (FSH and LH). Consequently, this chain of disturbances has negative effects on gonadal production of sex hormones (estrogens, progesterone and androgens), and thus on the reproductive system, causing irreversible damage to the HPG axis, impacting fertility and reproductive health in the long term. Sixteen studies have been carried out to investigate the link between exposure to BPA and hormonal disturbances in PCOS. A positive correlation between BPA hyperandrogenism was observed in 12 out of the 16 studies. Even independently of BMI, 15 studies reported high levels of BPA in women with PCOS. In addition, 6 out of 12 studies found a link between BPA and metabolic disorders (Urbanetz et al., 2024).

The agricultural environment and agricultural female workers can be particularly exposed to endocrine disruptive pesticides, such as dichlorodiphenyltrichloroethane (DDT) and glyphosate. This insecticide accumulates in human adipose tissue. Once in our bloodstream, they interact with hormonal systems, disrupting endocrine regulation (Darbre, 2017).

EDCs and their role in PCOS are described in detail in chapter II.

C. Metabolic and hormonal effects: long-term health consequences

As mentioned in chapter I-A, PCOS increases the risk of developing cardiovascular disease, as well as certain cancers, notably endometrial, breast and ovarian cancer.

Several conditions associated with PCOS favor the onset of heart disease, including insulin resistance, hyperinsulinism, abnormal lipid profile, coronary artery disease and hypertension. Insulin resistance is one of the main symptoms of the syndrome, in both obese and non-obese women. This low tissue sensitivity to insulin is offset by hyperinsulinism, which predisposes to type 2 *Diabetes mellitus*. According to Daniilidis A. & Dinas K., (2009), most women with type 2 diabetes under the age of 45 also have PCOS. Insulin resistance in women with PCOS also disrupts their lipid profile, with elevated levels of triglycerides and LDL cholesterol, and reduced levels of HDL, even in the absence of obesity. Furthermore, women with PCOS have elevated levels of a plasminogen inhibitor, which reduces the ability to dissolve blood clots, known as fibrinolysis, and can damage blood vessels and induce coronary heart disease, and complications cardiovascular. Finally, according to research, women with PCOS aged 40 to 59 have a prevalence of hypertension three times higher than women without the syndrome, supporting the fact that long-term PCOS leads to cardiovascular risks (Daniilidis A. & Dinas K., 2009).

Diet and weight play an essential role in the management and evolution of PCOS. More than half of PCOS patients is verweight or obese, which exacerbates hormonal and metabolic imbalances, such as insulin resistance, diabetes, hypercholesterolemia increasing the long-term complications associated with the syndrome. For these patients, weight reduction is often recommended as a therapeutic priority, combining a balanced diet with regular physical activity. To achieve this, it is recommended to do a moderate calorie reduction, equivalent to 30% of daily energy requirements, and an increased protein and fibre intake. Studies show that a weight loss of just 5% can help restore regular menstrual cycles and improve response to ovulation and reproductive stimulation treatments (Choudhari et al., 2024). A healthy lifestyle, based on a controlled diet and appropriate physical activity, is an essential approach to control que consequences of PCOS.

Therefore, PCOS and obesity have a complex, bidirectional relationship. While PCOS can contribute to insulin resistance and facilitate weight gain in women, obesity can also exacerbate the syndrome's symptoms. On the other hand, excess testosterone increases insulin secretion by the pancreas. This increase in insulin leads to insulin resistance and increases the metabolic disorders of PCOS, which can even increase the risk of developing associated diseases such as type 2 diabetes and cardiovascular disease. This leads to a decrease in Sex Hormone Binding Globulin (SHBG) secreted by the liver. SHBG is a protein that binds to sex hormones, such as testosterone, to limit their action. A decrease in this sex hormone-regulating protein leads to an increase in testosterone, and the "vicious circle" continues (Dason et al., 2024; Elise Rouvrais, 2021; Rosenfield & Ehrmann, 2016).

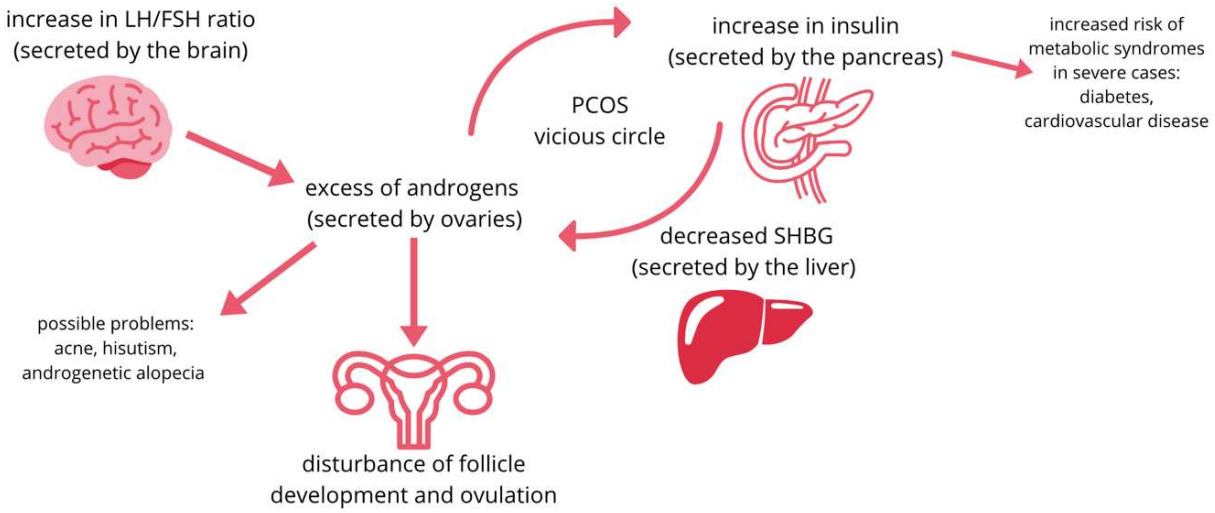

Figure 6 - The vicious circle of excess testosterone. Source: original based on Elise Rouvrais, (2021).

II. Endocrine disruptive chemicals (EDCs) and PCOS

A. EDCs and PCOS: How endocrine disruptors affect the hormonal system and ovarian function.

EDCs are defined by Srnovršnik et al., (2023) as "*An exogenous substance or mixture that alters the functions of the endocrine system and consequently causes adverse health effects in an intact organism, its progeny, or (sub)populations is referred to as an endocrine disruptor and this definition is frequently used.*" Similarly, the U.S. Environmental Protection Agency (EPA) defined the EDCs as *"exogenous agents that interfere with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process*." (Jozkowiak et al., 2023).

These chemical compounds, whether of natural or artificial origin, interfere with the endocrine system. Their mode of action depends on each case, but it is usually based on the imitation, inhibition or modification of hormonal signals, which can cause various physiological dysfunctions, even at low doses of exposure, particularly in sensitive populations such as fetuses and young children (WHO, 2013).

Human exposure to these chemical compounds occurs mainly through ingestion of contaminated food, but can also occur via inhalation of polluted air or dermal absorption (Srnovršnik et al., 2023). This endocrine-disruptive activity has been established in many chemical agents (such as BPA, phthalates, parabens, triclosan, and pesticides), in a variety of products, including packaging materials, compounds found in pharmaceutical and cosmetic products, and household products, as shown in Table 2.

Research is increasingly showing that EDCs are implicated in a variety of reproductive disorders in women. To date, they have been identified as having an impact on female and male fertility, contributing to the development of hormone-dependent cancers, such as breast and prostate

cancers. In addition, they play a role in the etiology of other diseases, including diabetes, obesity and cardiovascular conditions, some of them frequently associated with PCOS. This suggests a potential link between EDCs, PCOS and these metabolic disorders (Jozkowiak et al., 2023). Therefore, it is essential to investigate the role of EDCs in exacerbating hormonal imbalances in PCOS and its long-term implications in fertility and metabolic health. Recent research also showed that exposure to EDCs can also cause epigenetic changes. These changes can be passed on to subsequent generations, promoting an inherited predisposition to PCOS, such as hormone secretion and insulin sensitivity, suggesting that the exposure to certain EDCs during the prenatal period or prepubertal life could play a role in the manifestation of PCOS in adults (Jozkowiak et al., 2023).

The accumulation of lipophilic EDCs contributes to a vicious cycle that may, in the long term, exacerbate the symptoms of PCOS (Darbre, 2017). EDCs have a predominantly lipophilic structure, so these substances have an affinity for adipose tissue, where they can accumulate over the long term. This favors their storage in the body's fat reserves. In addition, some EDCs are implicated in metabolic alterations that promote fat mass increase, notably by disrupting the regulation of insulin and hormones involved in lipid metabolism. Islam et al., (2022) noted that "*chronic exposure to EDCs can lead to their accumulation in adipose tissue, potentially exacerbating their endocrine-disrupting effects over time*". Darbre (2017) supported these findings and referred that this accumulation can exacerbate various health problems specific to PCOS, such as hyperandrogenism, fertility problems, insulin resistance, *Diabetes mellitus*, and obesity and cardiovascular diseases. Also, according to Darbre (2017), the more adipose tissue, the more EDCs accumulate. On the other hand, obesity and overweight has been found to exacerbate the metabolic and ovulatory dysfunction reported in PCOS, and weigh loss often can restore ovulation and reduce hyperandrogenism in long-term (Islam et al., 2022) (Figure 8).

The accumulation of EDCs also promotes the retention of other lipophilic pollutants in adipose tissue and in amniotic fluid, breast milk, serum, and urine, thereby amplifying their harmful effects (Islam et al., 2022).

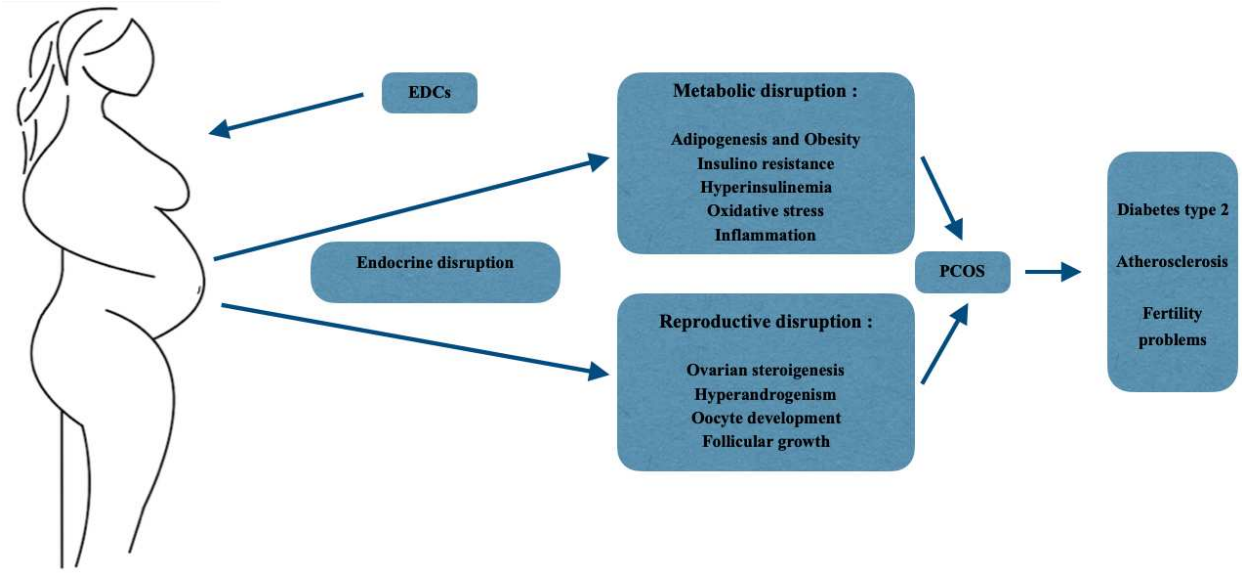

Figure 7 - Impact of exposure to EDCs on PCOS. Source: original based on A. Z. Rutkowska & Diamanti-Kandarakis, (2016).

Table 2 - EDCs and their uses. Source: original based on Islam et al., (2022).

Endocrine Disruptor	Sources of daily exposure
Bisphenol A (BPA)	Food packaging, epoxy resins, plastic products, household dust
Bisphenol analogues (BPS, BPF)	Plastic products, food packaging, everyday consumer items
Phthalates (DEHP)	Indoor dust, medical devices, food packaging, toys, cosmetics, kitchen utensils
Parabens	Personal care products, cosmetics, medicines, foods (as preservatives)
Triclosan	Personal hygiene products (soaps, toothpaste), household products, air fresheners
Organochlorine pesticides (DDT)	Food (contaminated fish, fatty meats, dairy products), contaminated environment
Perfluorinated compounds (PFAS)	Non-stick cookware, food packaging, waterproof clothing, textiles, water contaminated by industrial waste
Brominated flame retardants (BFRs)	Electronic devices, textiles, plastics, thermal insulation materials
Pesticides (Dichlorodiphenyltrichloroethane, Glyphosate, Chlorpyrifos, Atrazine)	Agricultural products, fruits and vegetables, pesticide-treated environments

Bisphenols

Bisphenol (BPA) is a synthetic organic compound widely used in the manufacture of polycarbonate plastics and epoxy resins. It is found in our daily lives in food contaminated by plastic packaging and in household dust. It is classified as an EDC because of its ability to mimic estrogen (Srnovršnik et al., 2023). BPA binds to estrogen receptors, disrupting the normal regulation of sex hormones. This binding alters the hypothalamic-pituitary-ovarian axis, leading to an increase in LH production and a decrease in FSH. The LH/FSH imbalance stimulates excessive androgen production by ovaries. In addition, BPA reduces the quantity of SHBG, increasing the amount of free testosterone in the blood (Urbanetz et al., 2023).

One study found that urinary levels of BPA were associated with an increased risk of type 2 *Diabetes mellitus*, with an odds ratio of 1.68, independent of BMI. This means that people with higher urinary levels of BPA are 1.68 times more likely to develop diabetes than those with lower levels (Anoop Shankar & Srinivas Teppala, 2011). Ben-Jonathan et al., 2009 explains this increased risk after BPA exposure because of increased adipocyte release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα). These pro-inflammatory cytokines contribute to the chronic low-grade inflammation associated with obesity and type 2 diabetes.

Bisphenol F (BPF) and Bisphenol S (BPS) are bisphenol analogues, which are also EDCsRochester & Bolden, (2015) referred that these analogues and BPA are very similar, both in chemical structure and hormonal effects. Like BPA, these substances have estrogenic, antiestrogenic, androgenic and antiandrogenic activities. Although initially created to replace BPA, they seem to present comparable health and environmental risks. Therefore, it is important to also consider their possible link to PCOS. As mentioned in chapter I-B, exposure BPA, and its analogues, can disrupt the HPG axis, due to the disruption of kisspeptin, reducing the release of FSH and LH (Urbanetz et al., 2024).

Rochester & Bolden (2015) also mentioned "*BPA is sometimes called a "weak" estrogen because of its relatively weak binding/activation of the nuclear receptors compared with [estradiol] E2,*

although this is not always the case". Although BPA can bind to estrogen receptors, but with a lower affinity than E2, this low affinity does not necessarily mean a weaker effect, since BPA can have significant effects even at low concentrations. Moreover, these authors mentioned that BPS can induce significant cellular effects via estrogen receptors, even at very low concentrations. Thus, BPS and BPF, are as hormonally active as BPA, suggesting that BPA would have similar effects at low concentrations.

EDCs such as BPA disrupt hormone regulation by altering the transmission of signals between the hypothalamus, pituitary gland and ovaries. This interference has a direct impact on follicular maturation, ovulation and hormone production. Exposure to EDCs alters the pulsatile secretion of GRH, promoting overproduction of LH and imbalance of the hypothalamic-pituitary-ovarian axis (Silva et al., 2023).

Phthalates

Phthalates are a group of esters of orthophthalic acid used as plasticizers to improve the flexibility of plastic materials. They are found daily in indoor dust, medical devices and food packaging. This EDC is also present in toys, cosmetics and kitchen utensils. Phthalates are widely used in the plastics industry, with worldwide production amounting to 4.9 billion kilograms per year (Silva et al., 2023). According to different studies, phthalates migrate from food packaging to food, entering the food chain. After exposure, phthalates can be found in several parts of the body, including amniotic fluid that surrounds the fetus in the uterus, and ovarian follicular fluid. This may indicate a constant exposure throughout life, including during embryonic development (Rutkowska & Diamanti-Kandarakis, 2016; Silva et al., 2023).

Animal studies conducted by Jin et al., (2019) have shown that exposure to di(2-éthylhexyl) phthalate (DEHP) is linked to alterations in the hypothalamic-pituitary-ovarian axis, which disrupts sex hormone levels, induces granulosa cell apoptosis, and impairs folliculogenesis, contributing to irregular menstrual cycles and infertility, commonly associated with PCOS. Moreover, *in vitro* experiments conducted by the same authors have demonstrated that DEHP exposure disrupts enzymatic activity by reducing CYP19A1 (responsible for converting androgens into estrogens)

and increasing CYP17A1 (involved in the production of androgens like testosterone). This hormonal imbalance leads to decreased estrogen levels and increased androgen levels, contributing to ovulatory dysfunction, polycystic ovarian morphology, and infertility, seen in women with PCOS.

Parabens

Parabens are found in certain personal care products, foods, medicines and cosmetics because they are alkyl esters of p-hydroxybenzoic acid used as antimicrobial agents and preservatives. They are considered EDC due to their antiandrogenic properties and its ability to affect thyroid function via its mimicry of the hormone estradiol, which enables it to link its receptors. Studies on the toxicity of parabens are not completely conclusive, but animal tests have shown that parabens cause histopathological changes in the ovaries. These alterations include an increase in the number of cystic follicles, thinning of follicular cells, and a drop in serum estradiol levels, seen in PCOS (Srnovršnik et al., 2023).

Triclosan

Triclosan is found in household, pharmaceutical, veterinary, industrial and personal care products, as well as air fresheners. He is recognized as an EDC due to its mimicry of the hormone estrogen, giving it a high affinity for estrogen receptors and resulting in estrogenic, antiestrogenic and antiandrogenic activities. Animal experiments showed a reduction in genes linked to antioxidation, leading to oxidative damage in the ovaries and ovarian apoptosis. These experiments also demonstrated a decrease in gonadotropin, progesterone and GRH levels, as well as mitochondrial toxicity, resulting in increased levels of estradiol and progesterone and promoting toxicological effects on steroidogenesis. Mitochondrial toxicity caused by triclosan stimulates estradiol and progesterone production by increasing cholesterol transport to the mitochondria, where it is converted to pregnenolone (a steroid hormone precursor) by the CYP450scc enzyme, and by

activating key enzymes involved in steroidogenesis (Faculte Medecine Dr Lamia Belacem, 2022; Srnovršnik et al., 2023).

Pesticides

Organochlorine pesticides (such as DDT) are found in the food chain in contaminated fish, fatty meats and dairy products. After ingestion, they accumulate in adipose tissue. They can alter fatty acid metabolism and mitochondrial function in hepatocytes. Exposure to organochlorine pesticides has been associated with metabolic disorders, notably obesity and type 2 diabetes (WHO, 2013). Organochlorine pesticides can alter metabolism via disruption of mitochondrial function by alternating the function of mitochondria in hepatocytes, resulting in increased oxidative stress. They also alter fatty acid metabolism by causing a decrease in fatty acid β-oxidation and an increase in the expression of genes involved in lipogenesis, thus promoting lipid accumulation in the liver. In addition, organochlorine pesticides can stimulate adipokine production by adipocytes, contributing to the development of obesity (Laila LAKHAL, 2018).

Certain organochlorine pesticides, such as DDT and its metabolites, have also been linked to disturbances of the female reproductive system, affecting the duration of menstrual cycles and circulating hormone levels. Experimental studies described by Kristen Upson et al., (2013) have shown that organochlorine pesticides can disrupt thyroid homeostasis in rodents and amphibians. DDT is an organochlorine insecticide, he acts as an estrogen by binding to hormone receptors, promoting hormonal disorders such as puberty in girls. DDT mimics estrogen and binds to hormone receptors. This can cause hormonal imbalances and problems with menstrual cycles and ovulation in women (Syed et al., 2023).

Other pesticides have been discussed and suggested as endocrine disruptors, including glyphosate and atrazine. Atrazine and glyphosate are two pesticides that may stimulate the aromatase enzyme, increasing the conversion of androgens to estrogens. This leads to hyperandrogenism and disrupts reproduction. Atrazine has also been implicated in the development of human cancers such as breast cancer (Fan et al., 2007; Richard et al., 2005). Glyphosate is a widely used herbicide, he

disrupts hormone receptor activity and estrogen production even at low doses (Vandenberg et al., n.d.).

Chlorpyrifos affects male and female reproduction by inducing dysfunctions of the reproductive system, notably by disrupting folliculogenesis and increasing the risk of metabolic disorders such as obesity ("HEAL-Chlorpyrifos," 2018). Methoxychlor has been shown to alter the function of enzymes involved in stereogenesis, such as CYP19A1 and CYP17A1. This EDC disrupts follicle development, leading to ovarian shrinkage and reduced fertility in rodents (Basavarajappa et al., 2011). In addition, studies suggest that methoxychlor may affect the male and female reproductive systems in humans, although this remains a theoretical concern (Stockholm Convention, 2021). Thus, these pesticides disrupt hormonal regulation and can exacerbate the symptoms of the syndrome.

PFAS and BFRs

Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS), are used for their resistance to water, grease and heat. They are found, for example, in non-stick Teflon cookware, food packaging, waterproof clothing and textiles, fire-fighting foams and water contaminated by industrial waste. Although published research did not explicitly establish a direct link between PFAS exposure and an increased risk of PCOS, the effects of PFAS on metabolism could contribute to the development of this syndrome. In fact, PFAS exposure has been associated with disturbances in lipid metabolism, an increase in total cholesterol, and insulin resistance (Julien Michaud-Tétreault et al., 2024).

Brominated flame retardants (BFRs) are chemical compounds used to reduce the flammability of consumer products. These compounds are found in electronic devices, thermal insulation, textiles and plastics. These substances are recognized as EDCs for their effects on the endocrine system (EFSA, 2024). Studies described by Fouikar, n.d. on female rabbits show that BFRs disrupt the hypothalamic-thyroid axis and ovarian steroidogenesis. For example, in female rabbits exposed for 17 weeks, abnormalities in follicular maturation and testosterone production were observed.

Although the long-term consequences remain to be clarified, these results underline the importance of limiting exposure to BFRs in at-risk populations such as pregnant women and young children.

Therefore, a continuous and prolonged exposure to EDCs may contribute to the worsening of PCOS symptoms over time, including hyperandrogenism, insulin resistance, and ovulatory dysfunction as shown in Figure 8. Furthermore, Silva et al., (2023) highlighted the importance of further studies to better understand the long-term impact of this exposure on PCOS, since most current studies focus on short-term exposure, without approaching the cumulative effects of chronic exposure, which could be more pronounced and relevant. Additional studies on long-term exposure to EDCs could help elucidate the mechanisms that aggravate PCOS symptoms and develop more effective prevention and treatment strategies (Barrett & Sobolewski, 2014).

B. The association between Bisphenol A (BPA) and PCOS: output from clinical published data

As presented above, BPA is perhaps one of the most well-studied EDCs in the literature, and therefore the relation between the exposure to BPA and PCOS is one of the most well-proved by the experimental studies. That is the reason why it was decided to dedicate a full subchapter to the clinical research data and evidence that can be found in the literature about this relationship.

Bisphenols (BPA and analogs) can affect steroid hormone production, as the increase of 17β-estradiol. As mentioned in chapter I, in PCOS there is already an imbalance between estrogen and androgen. Thus, a further increase in estradiol can further disrupt menstrual cycle regulation and ovarian function. Animal studies show that this estrogenic action can disrupt the normal menstrual cycle by excessively stimulating endometrial growth (Rochester & Bolden, 2015).

Eslami et al. (2017) assessed whether urinary concentrations of BPA were related to the presence of PCOS. The study compared two groups of women, a group of 51 women diagnosed with PCOS at a gynecology and infertility center, and a control group of 51 women consulting the same center for routine examinations. Results revealed a significant difference in the BPA level between two

groups, with a significantly higher level in PCOS group compared with control group (3.34±2.63 vs. 1.43±1.57 ng/mL, P<0.001). This observation showed that women with PCOS have higher urinary BPA concentrations than women in the control group. Logistic regression analysis confirmed this association, since BPA was considered the main dependent variable and significantly associated with PCOS (Odds Ratio (OR) = 1,53). This means that, after adjustment for other potential factors (age, body mass index, parity, menstrual irregularities, abortion history and education level), each unit increase in urinary BPA concentration is associated with a 53% increase in the probability of having PCOS (Eslami et al., 2017).

On the other hand, Srnovršnik et al., (2023) revealed higher levels of BPA in plasma, urine or follicular fluid in women with PCOS. Kandaraki et al., (2011) found higher mean serum BPA levels (1.05 ± 0.56 ng/mL) in women with PCOS compared to the control group (0.72 ± 0.37 ng/mL), as well as higher mean urinary BPA levels determined by Eslami et al., 2017b in women with PCOS (2.19 ± 1.88 ng/mL) compared to the control group (1.04 ± 0.98 ng/mL). Higher mean BPA concentrations in follicular fluid were also higher in women with PCOS (2.09 ± 0.12 ng/mL) in comparison with controls (1.04 ± 0.10 ng/mL) based on studies conducted by Wang et al., 2017.

Moreover, Srnovršnik et al., (2023) showed a positive correlation between BPA and free androgen levels, serum androstenedione and testosterone levels, insulin resistance, polycystic morphology on ultrasound, hepatic steatosis, bilirubin levels, and markers of chronic low-grade inflammation. This study presented the positive correlations between BPA levels and the free androgen index, as well as the positive correlations between BPA and serum levels of androstenedione and testosterone. Therefore, the Srnovršnik et al., (2023) confirmed an association between BPA and PCOS.

Zhou et al., 2016 described a negative correlation between BPA and ovarian follicle reserve markers in PCOS women. Jedrzejuk et al., 2019 showed a negative correlation between BPA levels and SHBG, and a negative correlation between BPA and vitamin D-binding protein, both in PCOS group women.

In addition to the previous studies, Rochester & Bolden (2015) explained how the antiandrogenic activity of BPA does not mean an improvement in PCOS symptoms. In fact, this disruption can further imbalance the endocrine system. In physiologically balanced conditions, estradiol and

progesterone help regulate the release of LH by sending a signal to the hypothalamus to decrease or halt its production. Under PCOS conditions, this regulatory mechanism appears to be impaired, probably due to a reduction in hypothalamic sensitivity to the inhibitory effect of estradiol and progesterone. These data suggest that elevated LH pulse frequency may arise from a reduction in hypothalamic sensitivity to estradiol and progesterone-negative feedback. Furthermore, studies indicate that hyperandrogenemia in PCOS patients may play a central role in the development and maintenance of this altered negative feedback. Decreased sensitivity to this feedback induces an over-frequent release of LH and thus an abnormal reduction in anti-androgenic hormones (Moore, 2022).

Moreover, some studies have been trying to find the limits of exposure to BPA that can be considered safe or tolerable to avoid PCOS and other endocrine diseases. Until 2015, Europe allowed, and the USA still allows, 50 µg/kg/day as the maximum daily exposure threshold for humans. Nowadays, this value is set much lower, at 0.0002 µg/kg/day, which reveals a higher precaution about this health hazard on human health (*Bisphénol A | EFSA*, 2023). Animal studies conducted by (Fernández et al., 2010) showed adverse effects at exposure levels close to the previously accepted reference dose for BPA (50 µg/kg/day).
Although human data on the exact thresholds for the appearance of BPA induced disturbances are lacking, these results from animal studies raise questions and concern about the impact of chronic, low-dose exposure on the human endocrine balance. Exposure to BPA occurs on a daily basis, since this compound can be found on products such as food packaging, cash register receipts and cosmetics. One study detected BPA in 80% of urine samples from the general population, indicating daily exposure (Patel et al., 2024).

Therefore, it is legitimate to ask what level of BPA exposure poses a significant risk for the development of PCOS. In other words, at what levels of BPA lead to a BPA accumulation sufficient to disrupt steroidogenesis, hormone signaling and metabolism (Patel et al., 2024a; A. Rutkowska & Rachoń, 2014). In view of the animal data and the absence of precise thresholds for exposure to BPA in humans, it is essential to consider the effects of daily exposure to BPA, even at low doses.

III. Therapeutic approaches to PCOS

A. Traditional therapeutic approaches to PCOS

The traditional therapeutic approaches to PCOS are considered in this way because they are the options most used by healthcare professionals, particularly the contraceptive pill, which is the first-line medication. What's more, their use goes back several decades, with well-documented clinical experience and safety. Their efficacy in treating and managing the clinical signs of PCOS is confirmed by numerous studies and medical recommendations, making them the cornerstone of PCOS management (Teede et al., 2023).

Hormone regulation and contraceptives pills (COCs, POCs and IUDs)

Combined oral contraceptives (COCs) are widely prescribed to correct hormonal imbalances associated with PCOS and alleviate its symptoms (Teede et al., 2019).

For instance, a study conducted by Di Carlo et al. (2013) treated 36 PCOS women with mild to moderate acne for 12 months with COCs pills containing dienogest and estradiol valerate (COC pill Qlaira®). After 12 cycles of treatment, an improvement in acne was observed in 52.8% of patients. The progestin dienogest acts by binding to progesterone receptors in the uterus, resulting in suppression of endometrial proliferation and progressive atrophy of endometrial tissue (Ruan et al., 2012).

Similarly, a study by Hoeger et al. (2008) evaluated the efficacy of COCs versus placebo in a six-month randomized clinical trial involving 20 adolescent girls. The results showed a significant increase in HDL in participants taking COCs. However, another study by the same author, involving 18 girls, and comparing the effects of COCs with those of lifestyle modifications, revealed that improved lifestyle habits were more conducive to LDL reduction. Thus, hormonal

COC treatment and lifestyle management are complementary to optimize lipid balance (Fitzpatrick et al., 2023).

Nevertheless, the choice of COCs must be tailored to each individual patient, considering their side effects. While high-estrogen formulations may be more effective, they also carry a greater risk of adverse effects. For this reason, it is recommended to prescribe COCs containing a low dose of estrogen as first-line treatment. COCs work through two mechanisms, the progestin component limits ovarian androgen production, while the estrogen component increases SHBG levels, reducing free androgens in the bloodstream. This results in an improvement in symptoms such as acne and hirsutism. (Teede et al., 2019).

Combined oral contraceptives containing drospirenone can improve the regularity of menstrual cycles and reduce circulating androgen levels, also helping to attenuate the clinical manifestations of PCOS (Bhathena, 2005). Drospirenone blocks androgen receptors while increasing SHBG, thereby reducing free testosterone levels. COCs pills associated with ethinylestradiol, such as Jasminelle®, Jasmine®, Yaz®, work with drospirenone to inhibit the release of LH and FSH, thereby suppressing ovulation and decreasing ovarian androgen production (Bachmann & Kopacz, 2009).

Cyproterone acetate combined with ethinyl estradiol, as in the Diane-35® pill, is also recommended for PCOS. Cyproterone acetate acts as an anti-androgen by blocking androgen receptors; it also inhibits LH secretion, which reduces ovarian testosterone production, helping to reduce symptoms such as acne and hirsutism. Ethinylestradiol complements this action by increasing SHBG, further reducing the free fraction of circulating androgens (Feng et al., 2016; VIDAL, 2025).

Thus, in brief words, COCs are often considered first-line therapy for women with PCOS without cardiovascular problems or insulin resistance, but with symptoms of acne and hirsutism (Amiri et al., 2020).

Progestin-only contraceptives (POCs), which do not contain estrogen, offer an alternative for women who cannot tolerate estrogen-based therapies or who have cardiovascular risk factors. In addition, estrogen-free hormonal contraceptives reduce the risk of endometrial cancer, a potential danger for women with PCOS due to prolonged exposure to estrogen without the protective effect

of progesteroneside effects of oral contraceptives include weight gain and nausea (Fitzpatrick et al., 2023; Oguz & Yildiz, 2021).

POCs with desogestrel as the active ingredient, such as the pills Cerazette® and Desogestrel Mylan®, contain no estrogen and therefore have a moderate anti-androgenic action, making them less likely to cause the hyperandrogenic symptoms of PCOS. Desogestrel alone inhibits ovulation while maintaining comparable levels of LH and FSH in serum (Dericks-Tan et al., 1992; J. Li et al., 2017). However, a study by (SM & A, 2012) 12-month comparative study shows that desogestrel reduces hirsutism less (Ferriman-Gallwey score: -1.69) than COC pills such as cyproterone acetate (Ferriman-Gallwey score: -5.29). POCs reduce acne and increase SHBG to a lesser extent than COCs.

POCs pills with drospirenone alone, like the Slinda® pill, are a safer therapy for estrogen-intolerant women, as is the desogestrel pill. Drospirenone directly inhibits ovulation by suppressing LH secretion (Archer et al., 2015). Drospirenone alone does not worsen insulin resistance or lipid profile, unlike some estrogen-containing COCs (Mathur et al., 2008).

COCs and POCs described above are ovarian pills that act primarily by inhibiting ovulation and modifying cervical mucus and the endometrium. Besides them, there are also intrauterine devices (IUDs) used to prevent pregnancy, such as hormonal (with levonorgestrel-releasing system) and copper IUDs. These act locally on the endometrium and cervical mucus, with less effect on ovulation. The hormonal device is composed of levonorgestrel and releases it into the uterine cavity, thickening cervical mucus, atrophying the endometrium and reducing sperm mobility (Baird et al., 2001; VIDAL, n.d.). The copper IUD works by releasing copper ions that are toxic to sperm, preventing fertilization and it can cause heavier, longer periods and more intense cramps, especially in the first months after insertion. Copper IUD is hormone-free and can last up to 10 years. The copper IUD remains an option for those who refuse hormones, although it has no effect on PCOS symptoms and the risk of expulsion of the copper IUD is particularly greater in younger women than in older women. Hormonal IUD release a small amount of levonorgestrel locally, which thickens cervical mucus, thins the endometrial lining, and may suppress ovulation. Hormonal IUD is often associated with lighter or absent periods and may cause spotting, breast tenderness, acne, or mood changes. It typically lasts for 3-8 years depending on the brand. The hormonal IUD is recommended in the presence of obesity, diabetes, cardiovascular problems or

contraindications to estrogen, offering metabolic security without aggravating insulin resistance. Both types of IUD are over 99% effective in preventing pregnancy (Hardeman & Weiss, 2014; Jatlaoui et al., 2017; Kaneshiro & Aeby, 2010).

Generally, for PCOS women, prescription of COCs with antiandrogenic progestins are a priority in cases of hyperandrogenic symptoms such as acne and hirsutism, and in the absence of cardiovascular and metabolic comorbidities, thanks to their antiandrogenic and cycle-regulating action. POCs pills are second-line pills for PCOS women at cardiovascular or metabolic risk, thanks to their safety. However, as mentioned POCs pills are less effective on acne and hirsutism and have less of an antiandrogenic effect than COCs pills (Amiri et al., 2020; Oguz & Yildiz, 2021). Side effects of oral contraceptives (COCs pills and POCs pills) include weight gain and nausea. COCs also carry thromboembolic risks (Kalman, 1969).

The final choice depends on the PCOS woman's prevailing symptoms and her choice considering their individual health needs and medical profile and the side effects associated with the proposed hormonal therapies (Amiri et al., 2020; Spritzer, 2022).

Antioxidants (vitamin D and myo-inositol)

A significant proportion (67-85%) of women with PCOS are vitamin D deficient. Kiani et al., (2022) highlighted the potential role of several natural molecules, including vitamin D and myo-inositol, in the management PCOS. These authors explained the positive association between vitamin D deficiency and other pathologies coexisting with PCOS, such as insulin resistance, type 2 diabetes, cardiovascular disease.

In fact, vitamin D regulates the glucose-insulin balance by activating specific receptors in the pancreas and muscles, directly stimulating expression of the gene involved in insulin sensitivity and energy metabolism. In addition, vitamin D appears to improve the metabolic and reproductive disorders of PCOS by acting on insulin resistance and fasting glycemia. Insulin resistance aggravates hyperandrogenism by stimulating insulin-induced androgen production by the ovaries. As a result, vitamin D, by acting on insulin sensitivity, improves androgen hormone regulation and thus reduces hyperandrogenism (Mohan et al., 2023; Sharon P et al., 2024). Given the high

prevalence of vitamin D deficiency in women with PCOS, and the positive results of vitamin D on insulin and androgen hormone regulation, vitamin D supplementation to be taken monthly in its cholecalciferol oral ampoule form is recommended for these women (Kiani et al., 2022).

Kiani et al., 2022 also reported that myo-inositol, a complex B vitamin, is an insulin sensitizer commonly used to alleviate the metabolic and reproductive disorders of PCOS. Women with PCOS taking myo-inositol supplements as an insulin sensitizer have had their ovarian function restored. The study conducted by A. Dinkova, 2017 mentioned that myo-inositol plays a major role in the regulation of hormones such as insulin, FSH and thyroid stimulating hormone, acting as a secondary messenger. Myo-inositol supplementation of 1 to 4 g per day reduces the LH/FSH ratio and improves menstrual regularity in 68% of patients (Mohan et al., 2023; Sharon P et al., 2024). The myo-inositol also has beneficial effects on oocytes in in vitro fertilization (IVF) patients and is effective in restoring ovulatory function, thus promoting fertility in PCOS patients (Armijo-Sánchez et al., 2024).

The vitamin D and myo-inositol combination potentiates the reduction of oxidative stress and inflammation, globally improving reproductive prognosis. Side effects are rare and manifest themselves as mild gastrointestinal disorders (Kiani et al., 2022). The recommendations are to target a serum vitamin D level below 30 ng/mL via daily or monthly supplementation, depending on the deficiency, and use a proportion of 40/1 myo-inositol/D-chiro-inositol formulation to optimize ovulatory restoration (Han et al., 2024; Kiani et al., 2022).

Thus, vitamin D and myo-inositol supplementation appear to benefit women with PCOS by improving insulin sensitivity, reducing hyperandrogenism and, at the end, improving ovarian function and fertility.

Metformin

Metformin is a dimethyl biguanide, an oral antidiabetic agent that acts primarily by decreasing hepatic glucose production and improving peripheral insulin sensitivity. Its pharmacological action is based on activation of adenosine monophosphate activated protein kinase (AMPK), a key regulator of energy metabolism (Attia et al., 2023).

Metformin, alone or in combination with COCs pills, helps managing weight and metabolism disorders, particularly in women with PCOS and with BMI ≥ 25 kg. In fact, metformin acts on several aspects of PCOS by improving insulin sensitivity. Since insulin stimulates androgen production in the ovaries, reducing insulin resistance reduces compensatory hyperinsulinemia and thus excessive androgen production by the ovaries. Metformin is also often used by women with PCOS to help regulate their menstrual cycle and improve ovulation, which can be a great help for those who have difficulty getting pregnant. In PCOS-related infertility, metformin would increase the success of fertility treatments. In addition to improving outcomes, metformin may reduce the risk of ovarian hyperstimulation syndrome, a possible complication of IVF (Attia et al., 2023; Johnson, 2014).

However, the effectiveness of metformin varies from person to person. Its use for PCOS is often done off-label and must be discussed with a healthcare professional on a case-by-case basis (Spritzer, 2022).The adverse reactions to metformin may include gastrointestinal disorders such as diarrhea (Froldi, 2024).

Clomiphene & letrozole

Clomiphene citrate, known as clomiphene, is a first-line treatment for amenorrhea in PCOS. Clomiphene is a selective estrogen receptor modulator, he acts by blocking estrogen receptors in the hypothalamus. This action disrupts the negative feedback of estrogens by preventing the decrease of FSH and LH. This stimulation of FSH and LH promotes follicular development and ovulation. However, clomiphene administration requires careful monitoring by ultrasound and blood tests to follow follicular development and endometrial thickness, determine the time of ovulation and prevent multiple pregnancies (approximate risk 8-10%) (Garthwaite et al., 2022). It is administered orally in tablet form, the initial dose is 50 mg/day for 5 days, starting between the 2^{e} and 5^{e} day of the menstrual cycle. Undesirable effects may manifest themselves via hot flushes, nausea, breast tenderness, dizziness, visual disturbances (Cunha & Póvoa, 2021).

Letrozole is also frequently considered for infertility treatment in PCOS (Collée et al., 2021). Letrozole is a triazole aromatase inhibitor, letrozole blocks the conversion of androgens to

estrogens and he is gradually replacing clomiphene as the first choice for PCOS-related infertility, thanks to its superior efficacy and safety. According to studies conducted by Legro et al., 2014, live birth rates were 27.5% with letrozole vs 19.1% with clomiphene, while ovulation rates were 61.7% with letrozole vs 48.3% with clomiphene (Legro et al., 2014). Initial dose of letrozol is 2.5 mg/day for 5 days, generally from day 3^{e} of the menstrual cycle, he is administered in oral tablet form (Guang et al., 2018). Side effects may include headaches, fatigue, hot flashes and nausea (VIDAL, n.d.).

The study of Mejia et al., (2019) showed that the combination of clomiphene citrate and letrozole is more effective than letrozole alone in inducing ovulation in women with PCOS. Ovulation rates were 77% with the combination of clomiphene citrate 50 mg/day and letrozole 2.5 mg/day. Ovulation results were 43% with letrozole alone (2.5 mg/day). This combination would enable follicle stimulation in PCOS patients resistant to monotherapies. This combination would be an effective and safe strategy for inducing ovulation in PCOS women, with a success rate almost double that of letrozole monotherapy.

Anti-androgens (spironolactone)

Spironolactone is normally used as an antihypertensive and diuretic drug. However, it is also been used off-label in PCOS due to its action as an antagonist of androgen receptors. In a few words, it prevents androgen hormones, such as testosterone, from binding and exerting their effects in different organs, working as an anti-androgen. It promotes an increase in SHBG, a protein that binds to free testosterone in the blood, thus limiting the amount of active hormone capable of stimulating androgen receptors. Consequently, it helps to reduce the symptoms of hyperandrogenism such as acne, excessive hair growth and hair loss. In addition, spironolactone accelerates the clearance of testosterone, resulting in decreased blood levels and reduced effects of hyperandrogenism in PCOS (Cumming, n.d.; Reiser et al., 2023).

Spironolactone was effective in reducing the Ferriman-Gallwey score, which evaluates hirsutism, with an improvement observed in 23 of the 30 women, according to G Shapiro & S Evron, 1980. On average, the score fell by 64% compared with initial values, and hair body quality improved,

becoming finer. Similarly, Cumming, n.d. have reported an improvement in acne, and studies suggest an effect on androgenetic baldness.

Recent studies now confirm its efficacy also in treating alopecia, with a systematic review from 2023 showing that after 6 months of treatment with oral spironolactone at a dosage of 25 to 200 mg/day, 80% of women reported an improvement in their hair density (C. Wang et al., 2023). Although spironolactone is now validated as a complementary option for treating alopecia, its topical 1% gel and 5% solution forms are safer than its oral tablet form. Minoxidil remains the gold standard for treating androgenetic alopecia, and will be discussed in detail in the following chapter (C. Wang et al., 2023).

Thus, spironolactone is a recommended treatment for patients with heart failure or high blood pressure. It reduces sodium retention, improves cardiac condition and lowers blood pressure. However, spironolactone has the side effect of hyperkalemia (increased blood potassium), and it is important to monitor patients with renal insufficiency (Georgianos & Agarwal, 2023).

Weight management

Barrea et al., 2023 highlighted the importance of nutrition and diet management in the prevention and treatment of PCOS, particularly regarding weight management. A 5-10% reduction in weight can improve reproductive function in women with PCOS, as well as reduce the risk of insulin resistance, heart disease (Wu et al., 2022).

Although there is not a specific and standardized diet for weight loss in women with PCOS, the adoption of a low-calorie diet is essential to achieve or maintain a healthy weight. Barrea et al., 2023 recommended reducing consumption of simple sugars, refined carbohydrates and saturated and trans fatty acids (Barrea et al., 2019). Barrea et al., 2023 also explores the role of different diets in the management of PCOS, including the Mediterranean diet, the low-glycemic index diet and the ketogenic diet. In fact, other authors have also verified significant improvements after a very low-calorie ketogenic diet (VLCKD) (Sawalha et al., 2023).

The VLCKD consists of a very low-calorie diet, with an intake of 600-800 kcal per day, or approximately 2500 to 3350 kJ per day. It limits carbohydrates to 30-50g per day, increases fats to 30-40 g per day, and calls for a slight increase in protein, around 1.2 to 1.5 g of protein per kilogram of body weight. Although the VLCKD diet has been shown to be effective in weight loss, improving insulin resistance and the LH/FSH ratio, it has side effects such as fatigue and constipation, as well as the risk of nutritional deficiencies (Barrea, Verde, Camajani, et al., 2023; Barrea, Verde, Schiavo, et al., 2023).

It is important to note that nutrition plans are used as a complement to pharmacologic approaches mentioned in this chapter. Moreover, they should be designed specifically for each patient, with a personalized approach, since each PCOS patient responds differently to each type of diet, and it must be adapted to the patient's lifestyle to make it feasible and sustainable (Mei et al., 2022).

B. Alternative therapeutic approaches to PCOS

Therapeutic alternatives include treatments that are not part of conventional care and often come from new research or complementary practices. While promising, it should also be pointed out that alternative approaches are not intended to totally replace traditional treatments, and many of these interventions have yet to undergo more robust scientific studies to prove their long-term efficacy and safety. Nevertheless, they can positively complement PCOS treatment, enabling a more multimodal and personalized approach that can be tailored to individual patient needs. The aim is to provide a comprehensive and up-to-date overview of the options available, emphasizing that the integration of different therapeutic approaches can provide better clinical outcomes for women with PCOS (Malik et al., 2024).

GLP-1 receptor agonists

GLP-1 receptor agonists are used mimic the GLP-1 hormone secreted by the intestine. They are normally used to stimulate insulin secretion in response to elevated blood glucose, reduce the

glucagon responsible for raising blood glucose, reduce appetite, slow gastric emptying and accelerate the feeling of satiety. As a result, they improve glycemia, reduce LDL and triglycerides, promote weight loss and lower cardiovascular risk. GLP-1 receptor agonists are more frequently used in type 2 diabetes and obesity patients. Nevertheless, considering their mechanism of action they can also be beneficial in NAFLD and PCOS, especially the ones that have obesity or type 2 diabetes (Bednarz et al., 2022).

Studies on overweight or obese PCOS women (BMI > 25 kg/m²) showed that 26 weeks treatment with the GLP-1 receptor agonist liraglutide reduced weight by 5.2 kg, liver fat, visceral fat and the prevalence of NAFLD. It also increased SHBG by 19%, decreased free testosterone by 19%, and lowered fasting blood glucose. The menstrual cycle improved, with treated women having almost twice as many menstrual cycles as those on placebo and ovarian volume decreased by 1.6 mL (Erguc et al., 2021; Hodges & Minich, 2015; Reinen & Vermeulen, 2015).

Cyproterone acetate (CPA)

Cyproterone acetate (CPA) is a steroidal anti-androgen that prevents testosterone and DHT from binding to androgen receptors and inhibits 5-alpha reductase, thus reducing the conversion of testosterone to DHT. In combination with ethinyl estradiol (EE), which increases SHBG, CPA reduces free testosterone, reinforcing its anti-androgenic effect. Thus, CPA (2 mg) combined with EE (35 µg) are mainly used to treat acne in women with hyperandrogenism (Bitzer et al., 2017).

In fact, studies have shown that CPA combined with EE is highly effective in improving skin lesions associated with non-inflammatory acne, such as comedones, and skin lesions associated with inflammatory acne, such as papules, pustules and nodules. Treatment with CPA+EE reduced the total number of acne lesions from 53.6% to 72% as early as three months. After six months, 90.2% of patients had shown an improvement in their acne (Carlborg, 1986; Palombo-Kinne et al., 2009).

Cytokine (interleukin-22)

Imbalances in intestinal microbiota have been identified in women with PCOS, as described in previous chapters. *Bacteroides vulgatus* is more abundant in women with PCOS. This increase in *B. vulgatus* is associated with a decrease in certain bile acids, which affects the proper functioning of the digestive system in women with PCOS (N et al., 2023).

Qi et al., 2019 demonstrated that transplanting the microbiota of women with PCOS or colonizing mice with *B.vulgatus* induces symptoms characteristic of PCOS in recipient mice, such as ovarian disorders, reduced insulin sensitivity, bile acid dysregulation and decreased levels of interleukin-22. Therefore, these authors proposed that supplementing women with PCOS with interleukin 22 can compensate for the decrease in beneficial bile acids, caused by *B. vulgatus*, improving these women's intestinal microbiota, ovarian function and insulin sensitivity. To suggest a potential treatment for PCOS via interleukin-22, the same study proposes different strategies for the administration of interleukin-22, such as direct injection of interleukin-22, adjustment of intestinal microbiota to reduce *B. vulgatus* and promote beneficial bacteria, and regulation of bile acid metabolism to stimulate natural interleukin-22 production. These approaches pave the way for new therapeutic avenues targeting the intestinal microbiota in the management of PCOS (Qi et al., 2019).

Drug targeting insulin resistance (SGLT2 inhibitors)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, a class of drugs that target insulin resistance, offer an alternative therapeutic approach for improving insulin sensitivity in patients with PCOS. These drugs function by inhibiting the SGLT2 in the kidneys, which normally reabsorbs glucose into the bloodstream. By blocking this glucose reabsorption process, SGLT2 inhibitors promote the excretion of glucose through urine, leading to lower blood glucose levels. This loss of glucose not only helps to reduce blood glucose levels but also contributes to weight loss by creating an energy deficit, forcing the body to draw on its fat reserves.

By promoting weight loss and glucose reduction, SGLT2 inhibitors improve insulin sensitivity, offering a promising approach to treating the metabolic imbalances of PCOS (Artasensi et al., 2023; Pereira & Eriksson, 2019).

Androgenetic alopecia treatments

In many cases of androgenetic alopecia, topical minoxidil 2% is the recommended treatment. Minoxidil is a pyrimidine-derived peripheral vasodilator that acts by opening potassium channels in vascular smooth muscle cells. Its action is based on stimulating hair follicles by prolonging the growth phase of the hair cycle, increasing follicle size and improving blood circulation to the scalp, thus promoting a better supply of nutrients and oxygen (WHITING & JACOBSON, 1992). The first visible results generally appear after four to six months of use. However, to maintain these benefits, treatment must be continued on an ongoing basis. If stopped, hair growth gradually ceases and the situation returns to its initial state (Herskovitz & Tosti, 2013; VIDAL, n.d.).

Prostaglandin analogues, such as latanoprost and bimatoprost, were initially used to treat glaucoma, and have been reported to have the side-effect of increasing eyelash growth. Prostaglandin analogues act by prolonging the anagen phase of the hair cycle. Their topical use on the scalp could therefore stimulate hair regrowth and increase hair density. However, their efficacy in treating androgenetic alopecia requires further clinical research to confirm their use in this indication (Khidhir et al., 2013).

Finally, 5-alpha reductase inhibitors block the enzyme responsible for converting testosterone to DHT, preventing the action of androgens on follicles, and thus slowing hair loss. Estrogens help neutralize the effects of androgens and promote hair regrowth (Hu et al., 2012).

Besides pharmaceutical therapy, laser and light treatments are also known to stimulate hair growth by improving blood circulation and stimulating hair follicles (Herskovitz & Tosti, 2013). If other treatments fail, hair transplantation can be considered. This involves removing hair follicles from areas with dense hair and grafting them onto balding areas (Herskovitz & Tosti, 2013).

Treatment options to eliminate or neutralize EDCs

The human body possesses complex enzymatic systems that modify and help dealing with EDCs. These transformations can either make them less toxic via detoxification or make them more toxic via bioactivation. Understanding these metabolic pathways is essential to developing effective strategies (Lauretta et al., 2019). Pharmacological treatments could be developed to specifically inhibit the enzymes responsible for EDC bioactivation and promote detoxification pathways by enhancing natural endocrine disruptor detoxification mechanisms via hepatic biotransformation and antioxidants.

Indeed, cytochromes P450 oxidize endocrine disruptors to make them more hydrophilic, and glutathione-S-transferase binds glutathione molecules (a natural antioxidant) to endocrine disruptors or their already oxidized metabolites, making them more water-soluble and facilitating their elimination by the body. No specific pharmacological treatment has yet been validated to inhibit EDC bioactivation enzymes or optimize their elimination in humans, although preliminary research is underway, thus, it would be interesting to develop pharmacological modulators of cytochromes P450 and glutathione-S-transferase. In fact they are promising for optimize hepatic and renal biotransformation, thus facilitating the biliary and renal elimination of EDCs (Bernal et al., 2024; Le Magueresse-Battistoni, 2021). It would also be interesting to look at antioxidants as an option for eliminating EDCs.

Antioxidants such as vitamins A, C and D neutralize the free radicals generated by endocrine disruptors, protecting cells and preventing oxidative stress from damaging DNA, lipids and proteins. Ogunlade et al. (2022) investigated testicular protection in rats, and concluded that vitamin C, vitamin A and vanillic acid attenuate the toxicity of the endocrine disruptor DEHP by restoring antioxidant levels (glutathione) and reducing lipid peroxidation. Vitamin D participates in the detoxification of endocrine disruptors by activating the expression of biotransformation enzymes, notably cytochromes P450 (phase I) and glutathione-S-transferase (phase II), thus facilitating their metabolization and elimination. Studies conducted by Kutuzova & DeLuca (2007), on vitamin D3-deficient rats, showed that this vitamin regulates hepatic detoxification pathways, suggesting its value in protecting against the harmful effects of endocrine disruptors in humans. According to data from animal models and *in vitro* studies, conducted by Bjørklund et al.

(2019), alpha-lipoic acid enhances hepatic detoxification capacity by stimulating glutathione synthesis, a key molecule in the neutralization and excretion of xenobiotics, including EPs. N-acetylcysteine is a well-established precursor of glutathione. Tenório et al. (2021) indicated that its supplementation increases GSH levels, boosting the antioxidant capacity of cells to eliminate toxins such as EDCS. The *in vitro* study of Geng et al. (2017) showed a protective effect of curcumin against BPA-induced insulin resistance. Curcumin acts by inhibiting the JNK and p38 MAPK signalling pathways, which are involved in inflammation and oxidative stress. By reducing these pathways, curcumin reduces the toxic impact of BPA on liver cells. Curcumin supplementation could therefore protect the liver against the metabolic and inflammatory effects of certain EPs such as BPA (VIDAL, 2025).

Dietary supplements containing the aforementioned antioxidants have already been developed, such as Detoxssentiel®. By combining these antioxidants, Detoxssentiel® offers an approach to support the body's detoxification mechanisms, particularly when it has been exposed to EDCs. This synergy aims to reinforce antioxidant defenses, modulate inflammatory responses and facilitate the elimination of environmental toxins. The components of Detoxssentiel® have been studied individually for their detoxifying efficacy, but there is no published research evaluating the efficacy of Detoxssentiel® food supplements. Clinical studies would be required to confirm the effectiveness of the synergistic effects of this product (VIDAL, 2025).

In the context of PCOS, gene therapy aims to correct the genetic abnormalities by identifying and correcting the genes involved in the syndrome. He et al. (2024) have identified ten genes as potential targets for gene intervention: CD93, CYBB, DOCK8, IRF1, MBOAT1, MYO1F, NLRP1, NOD2, PIK3R1 and PTER. These genes are involved in processes such as cytokine production, TNF signalling and immune regulation. Expression of these genes has been validated by qRT-PCR in animal models and serum samples from PCOS patients, confirming their potential role in the pathogenesis of PCOS.

Epigenetic alterations, such as DNA methylation and histone modifications, also seem to play a crucial role in the development of PCOS. Stener-Victorin & Deng (2021) have shown that epigenetic interventions can reverse certain phenotypes associated with PCOS.

Nanotechnologies also seem to offer promising solutions for the treatment of PCOS, notably through targeted drug delivery systems. Drug nano-delivery systems have been developed to improve therapeutic efficacy and reduce side effects in the treatment of disorders of the female reproductive system, including PCOS. The drug nano-delivery systems described by (van Staden et al., 2024) involve using nano-delivery systems to precisely target the female upper genital tract, thereby improving therapeutic efficacy while reducing side effects.

Enzyme inhibitors are molecules designed to specifically inhibit enzymes involved in a pathology. Research is underway to identify key enzymes and develop enzyme-specific inhibitors. A study developed by (Paulukinas & Penning, 2023) highlighted the role of the AKR1C3 enzyme in androgen production in women with PCOS. The study proposed that targeting this enzyme with enzyme inhibitors could reduce cardiometabolic disease associated with PCOS. Another study conducted by X. Li et al. (2021) reported that BVT.2733 acts as a selective inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase type 1. This enzyme is responsible for converting cortisone into active cortisol in tissues such as the liver, adipose tissue and ovaries. BVT.2733 inhibits this enzyme involved in PCOS symptoms, locally reducing cortisol production. This reduction in cortisol would lead to lower insulin resistance, improve hormonal imbalances and regulate the menstrual cycle of women with ovarian syndrome. Similarly to other underdevelopment approaches, these enzyme inhibitors pave the way for new possible solutions specifically targeting the key enzymes involved in the pathogenesis of PCOS, in order to inhibit their harmful effects.

Laser therapy

As mentioned in previous chapters, women in PCOS often present secondary diseases, as hirsutism and psychological depression. A study conducted on 80 women (between from 18 and 47 years old), who underwent 3 sessions of Laser-Assisted Hair Removal (LAHR), assessed the impact of laser therapy on the treatment on hirsutism, depression and quality of life of women (Hosseini et al., 2022). To do this, these authors used the e Ferriman-Gallwey, the Beck Depression Inventory and the Dermatology Quality of Life Index (DLQI) scores, respectively.

Before treatment, the hirsutism had a mean score was 7.05 (+/- 2.27) and decreased to 4.91 (+/- 2.41), bearing in mind that a score above 8 indicates hirsutism. Thus, this decrease in score shows a significant reduction in excessive pilosity. Regarding depression, calculated by the Beck Inventory, where a score closes to the maximum of 63 indicates severe depression, the mean score fell from 13.3 (+/- 8.7) to 10.2 (+/- 8.4), showing a psychological improvement. Dermatological quality of life (DLQI) also improved. Bearing in mind that the maximum score is 30 and indicates a significant negative impact, before LAHR, the score was 5.6 (+/- 5.2) and fell to 3.5 (+/- 2.3), reflecting a better quality of life for patients.

Therefore, the study concluded that LAHR could improve quality of life, depression and appearance in these hirsute women, considering positive changes in DLQI, Beck and Ferriman-Gallwey scores (Hosseini et al., 2022).

IV. Preventive strategies to reduce EDCs exposure

Exposure to EDCs, such as bisphenols, phthalates and parabens, is a growing public health concern due to their ubiquitous presence in our everyday environment and consumer products. Multiple toxicology and ecotoxicology studies have proved that these chemicals can disrupt the hormonal system, reproductive health and embryonic development, leading to different specific endocrine and reproductive diseases, including PCOS. Therefore, it is crucial to adopt prevention strategies to reduce exposure to EDCs, particularly during vulnerable life periods, such as pregnancy and childhood. The most promising approaches to prevent exposure and protect the most vulnerable groups are education and awareness-raising, promoting consumer choices that lead on substitution of toxic daily products, and adopting lifestyle habits that limit exposure to EDCs (WHO, 2013).

Education and awareness-raising provide individuals with the knowledge they need to make informed decisions (Kelly et al., 2020). Information campaigns should target common sources of exposure, such as food packaging, personal care products and baby toys. The public can be educated by labeling products containing EDCs, holding awareness-raising meetings on the subject in schools or displaying information in supermarkets ways (Pravednikov et al., 2024). The pregnancy prevention endocrine disruptors program (PREVED) aims to reduce pregnant women's exposure to endocrine disruptors through educational workshops. It improves knowledge and encourages safer behaviors - using glass containers and consuming less industrial products (El Ouazzani et al., 2021). Early detection of women at risk (prenatal exposure to EDCs or family history) and exposure reduction are essential preventive strategies. Stricter regulation of EDCs, along the lines of Europe's REACH regulation, would reinforce this approach (Endocrine Disruptors - ECHA, n.d.).

Good-quality information can indicate the presence of EDCs and give advice on the manipulation of products that may contain EDCs to avoid their release and contact, as not heating the food in plastic containers, keeping plastic water bottles away from light, not scratching non-stick frying pans, or avoiding direct contact with the skin for perfumes for example (Eales et al., 2022; Martin et al., 2022).

To adopt lifestyle habits that limit exposure to EDCs, it is important to avoid plastic containers and favor glass, stainless steel or ceramics for storing food and beverages (*Ways To Reduce Exposure to EDCs - HighPoint Health Center*, n.d.). Metal can linings often contain BPA, so to limit consumption of canned foods can also be considered a lifestyle change that protect the public. On the other hand, avoiding non-stick cookware containing PFAS, and preferring stainless steel, cast-iron or ceramic pans can also represent an individual protection measure. It's recommended drinking water from glass bottles or metal flasks, as some plastic bottles release micro-particles containing EDCs (Martin et al., 2022). As for fast food and ready meals, plastic packaging can contain phthalates and bisphenols, which can migrate from the plastic containers into the food. It is advisable to opt for fresh, organic and home-cooked foods, which would reduce exposure to BPA, and cut the levels of BPA metabolites found in urine by 66%, and 53 to 56% for phthalates metabolites (Corbett et al., 2022; Rudel et al., 2011).

Other habits can also be adopted daily to reduce exposure to EDCs. For instance, to choose organic food to reduce pesticide consumption from fruit, vegetables and meat, since some pesticides are also EDCs. People should choose cosmetics and hygiene products that are free from EDCs, by opting for products labelled "paraben-free", "phthalate-free" and "triclosan-free". Labels exist to identify these EDC-free certified products, such as COSMOS Organic, COSMOS Natural or ECOCERT which label natural or organic products (Martin et al., 2022). Certain EDCs are used in perfumes, such as phthalates, to fix scents. It's advisable to apply perfume to clothing, not directly to the skin, and to prefer natural perfumes based on essential oils or floral waters, or certified phthalate-free and paraben-free perfumes.

Moreover, people should avoid textiles and furniture chemically treated with BFRs or waterproofing containing EDCs. In household products, it is recommended to use natural cleaners such as vinegar-based cleaners, bicarbonate, or black soap (Rutkowska et al., 2020). Furthermore, it is important to pay special attention to toys and baby items, and make sure they are free of phthalates, BPA and BFRs. Considering all these measures, it is equally relevant to ventilate our homes regularly, approximately fifteen minutes per day, as EDCs like BFRs can be present in furniture, paints and candles, and build up in the indoor air (Eales et al., 2022; Martin et al., 2022).

Finaly, drinking water can also be an important source of different chemical pollutants, including EDCs. Also considering this, the WHO has set the maximum allowable pesticide concentrations in

drinking water (WHO, 2013). Home water filters vary in effectiveness at removing pesticides from drinking water, but cativated carbon and reverse osmosis filters are known to work best (Schreiber et al., 2024).

Conclusions and Future Perspectives

In conclusion, PCOS is a complex disease that can be associated to different metabolic, cardiac and reproductive consequences. Despite other predisposing factors, the association between EDCs exposure (including BPA) and the development of PCOS has been supported by the literature. Environmental exposure to EDCs is critical in the fetal programming of PCOS and its aggravation in adulthood. EDCs act by mimicking natural hormones and binding to their receptors, thereby disrupting their regulation and unbalancing the hypothalamic-pituitary-ovarian axis. This interference leads to overproduction of LH, which excessively stimulates androgen production by the ovaries, aggravating hyperandrogenism and its metabolic consequences. In addition, a chronic exposure to EDCs promotes their accumulation in adipose tissue, exacerbating the metabolic and hormonal disorders of a pre-existing PCOS.

Well-known treatments like estrogen-progestin pills, metformin, progestin, antioxidants, clomiphene and weight management are the most used for the management of PCOS in women. However, there is a need for constant improvement and, therefore, an opportunity for medical and pharmacological research to develop complementary treatments, specifically for certain clinical signs or secondary changes (as hirsutism or androgenetic alopecia).

Nevertheless, almost none of the available treatments address the association between PCOS and exposure to EDCs. The pharmaceutical and treatment industries could explore this link try to develop a treatment approach with this focus. Notwithstanding, there are already some underdevelopment treatments aimed to eliminate or neutralize EDCs in the body, such as drugs that block enzymes responsible for transforming EDCs into more toxic compounds, or molecules that improve detoxification pathways enhancing liver detoxification. Other innovative approaches are being developed, such as gene therapy, epigenetic therapy, nanotechnologies and enzyme inhibitor for EDCs.

For instance, epigenetic therapies could offer a promising prospect for correcting some cellular or DNA alterations caused by EDCs. This technology would help to correct the genetic abnormalities that contribute to the development of PCOS by regulating the expression of circRNAs involved in PCOS pathology and improving the development of reproductive and embryonic cells. In addition,

it could enhance the results of assisted reproductive technologies in women with PCOS who are trying to conceive a child (Gao et al., 2021). Moreover, the epigenetic therapies can reverse EDC-induced epigenetic modifications. DNMT inhibitors, such as azacytidine, can restore altered methylation profiles, while HDAC inhibitors, such as valproic acid, promote the expression of regulatory genes and miRNAs (Chen et al., 2024; Kobow & Khan, 2024). Gene and epigenetic therapies could, therefore, represent promising therapeutic avenues for PCOS by targeting the effects of EDCs. Nanoparticles may also provide a targeted detoxification method for women with PCOS, by capturing or degrading EDCs present in the environment and in the body. However, these approaches are not yet clinically applicable and require further research before they can be implemented (Chen et al., 2024).

Artificial intelligence (AI) can also be seen as a future prospect to quantify the risk of daily exposure to EDCs, create prevention labels for products and allow stricter monitoring of the regulation of EDCs. Thanks to machine learning algorithms using AI, it would be possible to rank the most ovarian-toxic EDCs by indexing extensive toxicological and clinical data. It might also be possible to anticipate interactions between pollutants and their effects on hormones.

Therefore, this work has provided a comprehensive overview of key aspects of PCOS, with a particular focus on therapeutic strategies, while highlighting the increasingly recognized role of endocrine-disrupting chemicals (EDCs) in its pathophysiology. We believe that a deeper understanding of this association paves the way for more targeted and personalized treatment approaches and that future of research in this field is promising. Although still in early stages, some new approaches show the potential to significantly transform PCOS management. Thus, this work reinforces the importance of a multidisciplinary approach to PCOS.

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