Review

Not peer-reviewed version

Current Updated Aspect Related to Pathogenesis, Diagnosis, Comorbidity and Management of Polycystic Ovary Syndrome—A Critical Review

Fauzia Tabassum , Chandra Jyoti , Khalid Orayj , Sultan M Alshahrani , Sirajudeen Shaik Alavudeen , Sadaf Farooque , Obaid Afzal , Nihal AlMuraikhi , Md Sayeed Akhtar *

Posted Date: 30 December 2024

doi: 10.20944/preprints202412.2399.v1

Keywords: Polycystic ovary syndrome; Comorbidity; Management; Quality of life; Pathogenesis

 doi:10.20944/preprints202412.2399.v1

Review

Current Updated Aspect Related to Pathogenesis, Diagnosis, Comorbidity and Management of Polycystic Ovary Syndrome—A Critical Review

Fauzia Tabassum [1,2], Chandra Jyoti [2], Khalid Orayj [3], Sultan M Alshahrani [3], Sirajudeen Shaik Alavudeen [3], Sadaf Farooque [4], Obaid Afzal [5], Nihal AlMuraikhi [6] and Md. Sayeed Akhtar [3,*]

[1] Department of Pharmacology, Vision College, Ishbilia, Riyadh 13226-3830, Saudi Arabia.
[2] Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, 751019, India.
[3] Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Al-Fara, Abha 62223, Saudi Arabia.
[4] Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj 16273, Saudi Arabia.
[5] Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj 16273, Saudi Arabia
[6] Stem Cell Unit, Department of Anatomy, College of Medicine, King Saud University, Riyadh, 11461, Saudi Arabia
* Correspondence: Author: sayeedpp@gmail.com

Abstract: The most common metabolic endocrine illness in women, polycystic ovarian syndrome (PCOS), swiftly impacts not only physical health but also psychological perception related to social and cultural ties that health-related quality of life (HRQOL). The HRQOL of women with PCOS is greatly affected by the constellation of symptoms that mainly accompany menstrual disorder and androgen excess. Several illnesses and conditions are more common in women with PCOS, such as obesity, insulin resistance, cardiovascular disease, infertility, cancer, and mental health issues. Managing the cases includes patient education, healthy lifestyle implementations, and the best possible therapeutic interventions, particularly based on targeting their symptoms. Therapeutic interventions include use of metformin, combined oral contraceptive pills, clomiphene citrate, spironolactone, surgery (ovarian laparoscopic drilling), and cosmetic interventions. Moreover, various new therapeutic approaches, such as use of inositol, statins, supplementation of vitamin D, miRNA therapy, interleukin-22 therapy, and faecal microbiota transplantation, bring new opportunities as well as challenges in PCOS management. This review will look at the different aspects of PCOS, other conditions that are linked to it, and the current and future ways that people with PCOS who are having trouble getting pregnant can improve their quality of life.

Keywords: Polycystic ovary syndrome; Comorbidity; Management; Quality of life; Pathogenesis

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder having multiple etiologies that distresses between 8–13% among women of ovulatory age worldwide. Importantly, approximately 70% of diseased women remain undiagnosed, and their lives remain compromised [1]. PCOS has a complex origin involving genetic, environmental, and lifestyle factors, and many more are still debated. It is recognized as elevated levels of androgens, irregular menstrual cycles, resistance to insulin, and polycystic ovaries [2,3]. Numerous women with PCOS experience feature of the

 doi:10.20944/preprints202412.2399.v1

metabolic syndrome, together with insulin resistance (IR) and raised insulin levels. High androgen levels, a key feature of PCOS, have significant health impacts on the young female population.

Hirsutism, acne, and male pattern alopecia are some of the clinical signs of hyperandrogenism (HA). In around 20% of PCOS instances, chronic anovulation manifests as irregular menstrual bleeding, irregular menstrual periods, or infertility that occurs at the same time as similar to women with regular menstrual cycles [4,5]. Clinically, 50–80% of females with PCOS are obese, 30–35% have impaired glucose tolerance, and 8–10% have diabetes melitus [2–4].

PCOS has been found to be a major concern for women's health, particularly impacting health-related quality of life (HRQOL). It is worth revealing that PCOS upsurges the odds, such as cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2DM), and other metabolic syndromes concurrent to psychological distress, and puts women in serious life-threatening conditions [6–8]. The hormonal changes-based pathogenesis of PCOS involves elevated levels of the gonadotropin-releasing hormone (GnRH) from the hypothalamus that lead to excessively increased levels of the luteinizing hormone (LH) and lower levels of the follicle-stimulating hormone (FSH). This hyperstimulates the ovaries to secrete additional androgens and leads to ovulatory dysfunction. Another cause of PCOS is an endocrinological disturbance of the insulin axis, such as hyperinsulinemia and IR. Higher circulating levels of insulin diminish the secretion of sex hormone-binding globulin (SHBG) from the liver, which in turn elevates the free testosterone in body circulation and develops characteristics of hyperandrogenemia [9–11].

As the pathogenesis of PCOS is quite complex, the treatments must be individualized according to current signs and symptoms and require multiple drugs to manage the disease. Noteworthy, the United States Food and Drug Administration (USFDA) yet did not approve drugs explicitly for PCOS, and only off-label drugs are available for managing this condition. To manage PCOS, the most important step is to reduce at least 5% of the body weight. Thus, a healthy diet and regular exercise plan are well recommended for every woman with PCOS [12]. Moreover, all the management needed to revisit for improving the HRQOL among PCOS patients.

2. Pathogenesis and Clinical Manifestations in Polycystic Ovary Syndrome

There are a number of variables that are linked to the pathophysiology of PCOS, characterized by the interplay between endocrine secretions, genetic morphology, and ecological stressors (Figure 1).

 doi:10.20944/preprints202412.2399.v1

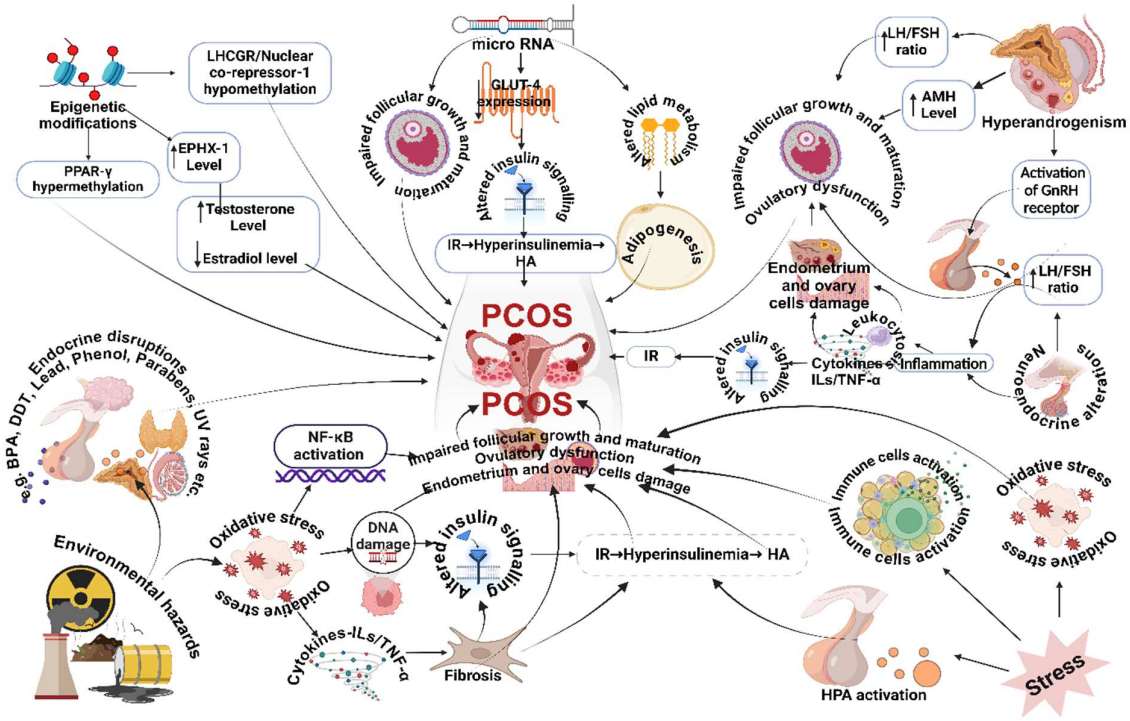

Figure 1.

Hyperandrogenism

Generally, HA develops due to decreased sex hormone-binding globulin (SHBG) levels and raises the free testosterone concentration in PCOS. Elevated amounts of testosterone in plasma can be transformed by adipose tissue into estrone. When the process of converting estrone to estradiol is interrupted, it affects follicular growth as well as changes the ratio of LH to FSH, leading to ovulatory failure [13,14]. Additionally, HA increases anti-mullerian hormone (AMH) levels, which suppresses follicle development and ovulation via various processes [15]. Moreover, HA is inversely correlated with IGF-II levels, which favorably influence follicle diameter and estradiol concentration in follicular fluid [16]. LH levels are indirectly raised by HA. Through negative feedback processes, progesterone and estradiol both regulate the secretion of GnRH and LH. This negative feedback loop gets disturbed by HA and raises LH levels [17]. Progesterone receptor transcription is hampered by androgen's interaction with its receptor. Raised androgen levels are linked to changes in GABA-A receptors, activate GnRH neurons, and lessen the body's reaction to the negative feedback mechanism of progesterone [18]. Furthermore, androgens can lower hepatocyte nuclear factor 4 (HNF-4) levels in the liver by blocking lipogenesis, and they also bind to the promoter of SHBG to increase its expression [9]. Other PCOS variables like inflammation, oxidative stress, and IR are facilitated in their advancement in HA [19]. It increases IR via a number of mechanisms, including lowering GLUT-4 expression, insulin sensitivity, and suppression of hepatocyte insulin degradation [20]. Adipocyte enlargement is mostly caused by HA, which also markedly reduces adipokine secretion [21]. These facts suggest that PCOS patients typically have high levels of circulating androgens; it is imperative to comprehend the involvement of hyperandrogenemia in the pathogenesis of PCOS-related abnormalities.

Neuroendocrine Implications

As evidenced, PCOS is reported as a disorder of neuroendocrine origin and mental health disorders, including mild to severe symptoms related to anxiety, depression, eating disorder, and even bipolar disorder [17,22]. Many studies suggested that changes in Gamma Amino Butyric Acid

 doi:10.20944/preprints202412.2399.v1

(GABA) activity and its level affect the hypothalamus-pituitary-gonadal (HPG) axis (stress axis) and cause development of PCOS [23–25]. When taken as a whole, these results highlight the possibility that the neuroendocrine axis plays a role in PCOS development. The data suggests neuronal involvement in the neuroendocrine trails contributing to PCOS. This will be highlighted by studying the involvement of GABAergic neurons.

GABAergic Neurons

GABA neurotransmitter acts primarily as inhibitory in nature stimulates GnRH neurons rather than inhibiting them because of their high intracellular chloride content. GABA-A receptor helps GABA to activate GnRH neurons. Evidence indicated that cerebral fluid of women with PCOS has greater than normal concentrations of GABA [26]. Thus, increased generation of GnRH in PCOS partially enlightened by the reported rise in GABA levels, but this is still conjectural [27,28]. Study suggests that GABA may have dual excitatory and inhibitory nature on different cell groups in the brain. A reduction in GABA levels may lead to an increase in the activity of afferent neurons that are responsible for activating GnRH neurons (Kisspeptin neurons). Kisspeptin functions as a strong inducer for the release of GnRH. High blood levels of LH and circulating kisspeptin are positively correlated among women with PCOS [29,30]. It has been suggested that PCOS may be influenced by kisspeptin neurons since kisspeptin normally stimulates GnRH neuron. Furthermore, the increased LH secretion and GnRH neuron activity are supported by increased Kiss1 mRNA expression in PCOS [31]. Ovulation and blood levels of testosterone or LH after therapy, however, were not assessed over the long term. In women with PCOS, metformin, OCP, dexamethasone, flutamide, and rosiglitazone reduced biochemical hyperandrogenemia, but their side effects may limit their use. [32]. Androgens, rather than decreasing negative feedback and encouraging higher GnRH/LH secretion, would be predicted to elicit more negative feedback, resulting in lower GnRH/LH release. In fact, androgen treatments further decrease the synthesis of GnRH by reducing Kisspeptin 1 (Kiss1) levels in addition to LH secretion in vivo [23,33]. The discrepancy related to the negative feedback process of androgen activities and future research that suggests androgens have a potential role in promoting the hypersecretion of GnRH in PCOS has to be addressed.

MicroRNA

Recently, much evidence about the pro-therapeutic benefits of microRNAs (miRNAs) has been demonstrated for various disorders, together with PCOS [35–37]. Gene expression is regulated after transcription by miRNAs, short non-coding RNAs attached with around 22 nucleotides. These miRNAs specifically target genes of the 3′ untranslated region (UTR) and impede their translation, concurrently developing instability [37]. miRNA interaction with target messenger RNA (mRNA) leads to mRNA splitting, obstructing translation, and mRNA degradation [38]. Several physiological processes, such as cell differentiation, proliferation, inflammation, and apoptosis involve various short RNA molecules [36]. Even individual miRNA has the ability to influence the diverse alterations in functioning of diverse target genes responsible for PCOS pathogenesis. The intensification or suppression of a miRNA-generated signal substantially alters the miRNA expression through regulatory feedback mechanisms. This change is an add-on in the initiation and progression of many diseases, like diabetes mellitus, cardiovascular disease, endometriosis, and ovarian cancer [39–43]. This aberrant miRNA expression is thought to have a pivotal role in the progression and development of the PCOS. It further regulates the production of steroidal hormones, impacts the growth and follicular maturation, adipocytes enlargement, and modulation of insulin signaling. In the context of PCOS, miRNAs play a pivotal role in inflammatory processesn, reduced ovarian insulin sensitivity, hyperinsulinemia, and compromised oocyte quality [36,40]. Gaining a comprehensive relationship between miRNAs, steroid hormone production and related metabolic abnormalities suggest the potential to assist in PCOS pathogenesis [44]. In addition, influencing the GLUT4-associated miRNA expression has potential role in controlling glucose metabolism, the insulin signaling system, and the development of IR in PCOS [45]. The impact of microRNAs on lipid

 doi:10.20944/preprints202412.2399.v1

metabolism is well discussed, and it seems that microRNAs such as miR-128-1, miR-148a, miR-185, and miR-375 is well associated with metabolism of LDL-C, adipogenesis, increased body mass index (BMI), and possesses aberrant expressions in PCOS conditions [46,47].

Environmental Stressors, Epigenetic Mechanisms, and Xenobiotics

Multiple genetic and environmental variables contribute to the development of PCOS illness. An imbalance of free radical generation and antioxidant systems is also recognized as a possible factor contributing to PCOS initiation and progression [48,49]. Moreover, several studies indicate that prenatal exposure to androgens may have a role in the emergence of PCOS at the fetus stage itself [50,51]. According to the United States Environmental Protection Agency (USEPA), a range of chemicals called endocrine-disrupting chemicals (EDCs) hinder the synthesis, release, movement, attachment, or elimination of natural hormones responsible for metabolic homeostasis, growth, reproduction, and mental behavior. It is beyond a shadow of a doubt that even little disruptions in endocrine function, especially at some extremely sensitive periods of the lifecycle (for example, child growth, pregnancy, and breastfeeding), may result in significant and long-lasting repercussions [52,53]. Common EDCs like bisphenol A (BPA) are frequently used in plastic industries for manufacturing dental fillings, food and beverage packaging, infant bottles, and polyvinyl chloride. These substances disrupt metabolic processes via various mechanisms. BPA has a direct effect on the process of the formation of ovum by modulating estrogen receptors (ER), non-classical membrane ER, and G-protein-coupled receptor 30. In theca cells, it stimulates the production of androgens and prevents the breakdown of testosterone [54,55]. In addition, BPA has an effect on the adrenal cortex and gonad endoplasmic reticulum-resident enzyme CYP17, which is implicated in the production of glucocorticoids and sex hormones by mediating the 17a-hydroxylase and 17,20-lyase reactions of progesterone and pregnenolone [56,57]. BPA has the ability to decrease the expression of the aromatase enzyme and the generation of estrogen in granulose cells. This eventually leads to the disruption of the environment around the follicles and the halting of oocyte development as well as maturation [58]. BPA indirectly raised testosterone levels via diminishing the functioning of testosterone 2a-hydroxylase and testosterone 6b-hydroxylase enzymes in liver cells [59]. It further displaces testosterone from SHBG, leading to raised serum testosterone levels [60]. Due to PCOS's clinical variability, it is now widely understood that environmental stressors such as EDCs seem to disrupt several neuroendocrine, hormonal, and metabolic signaling pathways, making them a potential environmental cause of PCOS.

Stress

Although the exact link between stress and PCOS is not well documented, it is established that PCOS may have negative impacts on self-esteem and mental well-being. Extended stress induces the excessive proliferation and expansion of fat cells, initiated by excessive release of glucocorticoids and their effect on the maturation of immature fat cells [61,62]. Stress may have detrimental consequences for the body, including the release of adipokines, the attraction of immune cells to adipose tissue, and their activation of these immune cells [63]. Stress-mediated raised glucocorticoids level triggers inflammation, as evidenced by raised cytokines such as IL-6 and TNF-α, and this interferes with the functioning of free radical scavanging enzymes [64]. Stress has a detrimental effect on the hypothalamic-pituitary-adrenal (HPA) axis, causing the release of cortisol. In turn, cortisol promotes the accumulation of fat in visceral organs as well as the processes of IR, gluconeogenesis, and lipolysis [65]. Importantly, stress is itself linked to the excessive release of insulin in the bloodstream. Additionally, stress-related variables include disruption of AMH and altered reproductive hormone in PCOS patients [66,67]. Stress-related PCOS includes metabolic, inflammatory, oxidative, and mental stress, and its pathophysiological core appears early in life. Metabolic stress causes long-term health problems that worsen the syndrome's reproductive, metabolic, and psychological derangements, creating a cycle of chronic sickness.

 doi:10.20944/preprints202412.2399.v1

Epigenetic Mechanism

Epigenetic alterations include the process of adding or removing chemical constituents from DNA or histone proteins. PCOS cases often display excessive activity of LH, associated to hirsutism and dysfunctions in the formation of ovarian follicles and hirsutism [68]. The production of steroids in theca cells is controlled by LH/choriogonadotropin receptor (LHCGR) [69]. Because of hypomethylation of LHCGR, there is an elevation in gene expression and an increase in LH sensitivity [68,69]. The hypomethylated sequences are linked to the increased expression of LHCGR on the surface of theca cells. Moreover, the enzyme Epoxide Hydrolase 1 (EPHX1) plays a vital role in breaking down aromatic chemicals [70,71]. Overproduction of EPHX1 hampers the conversion of testosterone to estradiol, hence playing a role in the development of PCOS. Peroxisome proliferator-activated receptor gamma (PPAR) plays a crucial role in maintaining normal ovarian function [72,73]. In PCOS women, hypermethylation of PPAR, hypomethylation of nuclear co-repressor 1, and changes in the acetylation of histone deacetylase 3 are well evidenced in the pathogenesis of PCOS [74].

Insulin Resistance

In women with PCOS, IR affects specific tissues such as skeletal muscles, adipocytes, and hepatocytes, which lose their sensitivity to insulin. However, the adrenal gland and ovaries maintain their sensitivity to insulin. Insulin has a direct influence on the generation of androgens and the formation of follicles in the ovaries [75]. On the other hand, an excess of insulin in the body decreases the levels of SHBG in the liver, which leads to a reduction in the synthesis of insulin-like growth factors (IGF-1)-binding proteins and raised androgen production in theca cells [76]. Reduced expression of IGF-1 makes the survival of granulosa cells difficult and thus the process of folliculogenesis, resulting in hindered development of follicles owing to both excessive androgen levels and high insulin levels [76,77]. Hyperinsulinemia due to IR has a negative impact on the pituitary gland by endorsing the release of LH and altering the production of GnRH (Tosi et al., 2012). Additionally, insulin is involved in the processes of adipogenesis, lipid synthesis, and fat storage [75]. IR increases the concentration of fatty acids in the bloodstream, which has a direct effect on the liver and adipocytes and triggers the building of masculine body features [78].

Inflammation

When it comes to ovulation and folliculogenesis, cytokines play a crucial role in regulating ovarian physiology by helping to establish conditions favorable to follicle selection and development. They control cell proliferation, differentiation, and maturation of oocytes [79,80]. Leukocytosis, raised levels of C-reactive protein (CRP), and other inflammatory mediators such as interleukins (ILs) in the stream remain associated with PCOS development [81–83]. Moreover, HA also significantly contributes to inflammatory processes [82]. TNF-α, a prominent pro-inflammatory cytokine, worsens IR by disrupting insulin signaling pathways, leading to a decrease in the expression of GLUT-4. IL-1 further hinders the manifestation of FSH and LH receptors, reducing the growth of follicles and the occurrence of ovulation [84,85]. TNF-α and IL-1 impede hepatic nuclear factor (HNF) activation in diverse ways. In addition, nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing proteins-3 (NLRP3) inflammasomes trigger pyroptosis in follicular cells, contribute to ovarian fibrosis, and interfere with the development of follicular cells [86]. The genetic polymorphism study also indicated the involvement of interleukins and other inflammatory mediators in the development of PCOS [87,88].

Oxidative Stress

Oxidative stress is characterized by an overproduction of highly reactive free radicals that is not neutralized by antioxidant systems [89]. Both reactive oxygen species (ROS) and reactive nitrogen species (RNS) are directly or indirectly involved in various signaling cascades (Lai et al., 2018),

 doi:10.20944/preprints202412.2399.v1

cellular growth, and differentiation [90,91]. Furthermore, ROS/RNS have an impact on the functional physiology of the ovaries, which includes the process of steroidogenesis and even change in eating behavior [92,93]. The overproduction of ROS/RNS, on the other hand, has been shown to be detrimental to essential molecules such as deoxyribonucleic acid (DNA), lipids, and proteins [89,94]. Nuclear factor-kappa B (NF-κB), which is connected with a number of different inflammatory pathways, is stimulated by increased oxidative stress, which alters the production of pro-inflammatory cytokines like TNF-α and ILs [95,96]. These free radicals further develop IR through suppressing the insulin signaling cascade via these inflammatory markers, leading to enlarged adipocytes and obesity. In turn, this furthermore initiates the physiological and psychological complexities related to PCOS [75]. Several evidences have shown that the etiology of PCOS is associated with elevated levels of oxidative stress [48,79,97].

Obesity

Obesity is a significant cause for developing chronic inflammation [98,99]. Subsequent necrosis is caused by the overdeposition of adipocytes and lipids in visceral organs, which in turn triggers the further release of inflammatory cytokines [100]. Adipose cell hypertrophy and abdominal fat accumulation relate to the onset of an inflammatory condition [100,101]. In addition, obesity has a role in the development of both IR and HA. Elevated levels of non-esterified fatty acids (NEFAs) in the body's circulation cause visceral adeposity and thus obesity [102,103]. Skeletal muscles preferentially use NEFAs as an energy source rather than utilizing glucose. This hyperglycemic condition triggers the pancreas, resulting in hyperinsulinemia. In addition, visceral fat and catecholamines stimulate the breakdown of fats, leading to lipotoxicity and hindering the removal and effectiveness of insulin [104,105]. Higher levels of free fatty acids (FFAs) lead to a reduction in glucose sensitivity and insulin absorption inside muscle cells, resulting in lower intramyocellular lipid levels [75,106,107]. Research has shown that women with a genetic predisposition to developing PCOS commonly undergo these many clinical and biochemical changes as a result of gaining weight and becoming obese, suggesting a strong link between obesity and the development of PCOS [108–110].

Diet

While there is a lack of definitive information addressing the involvement of diet in PCOS, earlier research has shown a correlation between diet intake and diagnostic markers of PCOS [111–113]. Saturated fatty acid (SFA) intake has been associated with the development of PCOS via overproduction of inflammatory cytokines, decreasing insulin sensitivity, and increasing IR [114,115]. Saturated fatty acids generate inflammatory markers like TNF-α in the blood and activating genes that repress production of certain cytokines [116]. Importantly, vitamin D deficiency worsens PCOS and its associated health conditions [117–119]. Calcitriol increases the expression of insulin receptors at both the mRNA and protein levels. This leads to a direct and indirect improvement in insulin sensitivity. The indirect impact refers to the activation of PPAR-γ, metabolism of fatty acids in adipocytes, and skeletal muscles. On the other hand, a lack of vitamin D is linked to IR mediated by the generation of inflammatory markers. Furthermore, there have been reports indicating that deficiency in vitamin D might decrease the activity of the anti-müllerian hormone (AMH) promoter [117–119].

3. Clinical Features Related to Polycystic Ovary Syndrome

Clinically, PCOS-related features have been categorized into three groups: reproductive, psychological, and metabolic features (Figure 2). Reproductive features include hirsutism, HA, menstrual and ovulation dysfunction, pregnancy difficulties, infertility, gestational diabetes, chances of miscarriage, preeclampsia, endometrial hyperplasia, as well as neonatal morbidity. Psychological

 doi:10.20944/preprints202412.2399.v1

features include anxiety, poor self-esteem, depression, and compromised HRQOL. Metabolic features include IR, dyslipidemia, T2DM, impaired GTT, and risk of CVDs [120].

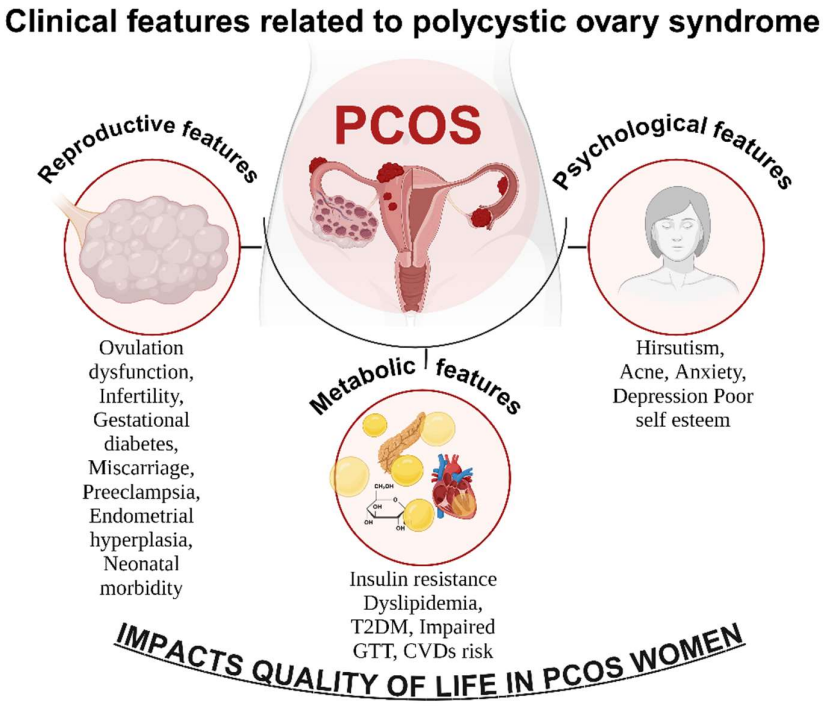

Figure 2.

4. Major Co-Morbidities Related to Polycystic Ovary Syndrome

Many eminent institutions, like the Endocrine Society, the Androgen Excess and PCOS Society, and the American College of Obstetricians and Gynecologists, have concluded that clinicians should be recommended to evaluate patients' blood pressure, OGTT, obstructive sleep apnea, depression, and mood disorders at the time of diagnosis and at every subsequent visit [120,121]. PCOS is often associated with multiple alterations, primarily metabolic syndrome, which has been reported to have major associated co-morbidities (Figure 3).

 doi:10.20944/preprints202412.2399.v1

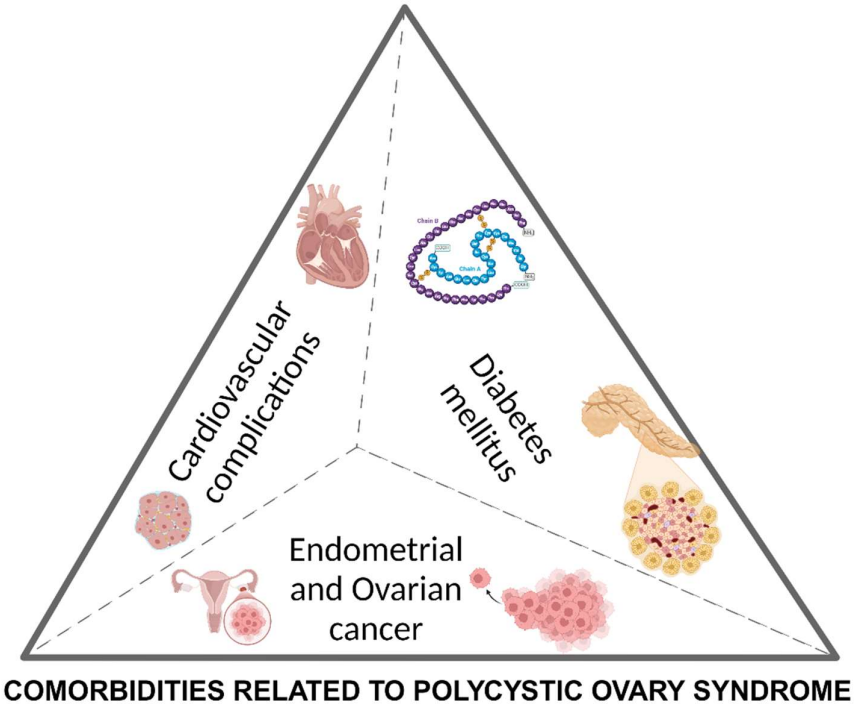

Figure 3.

The study suggests that once a woman gets diagnosed with PCOS, the risk for her developing T2DM also increases by up to four times [122,123]. Additionally, an elevated risk of mood disorders among the patients diagnosed with PCOS is well evidenced [124–126]. All the important risk factors related to PCOS has been depicted in Figure 4.

 doi:10.20944/preprints202412.2399.v1

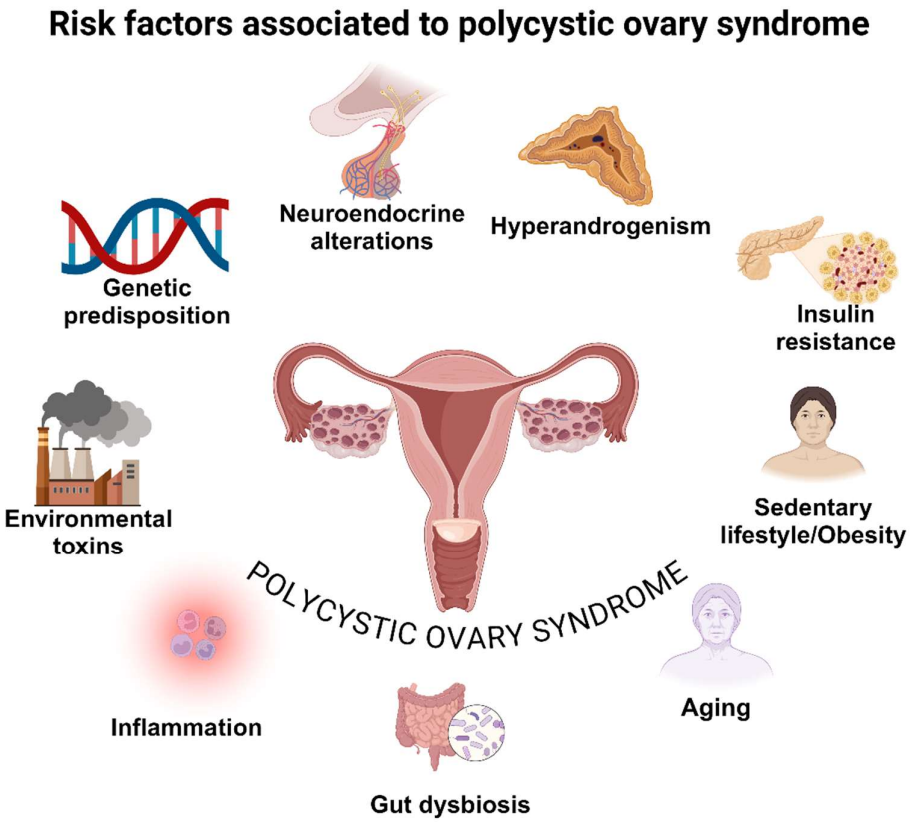

Figure 4.

Cardiovascular Disease and Dyslipidemia

As reported, the leading cause of death for women is CVDs among those suffering from PCOS [127]. The core risk factors associated with increased CVDs include central obesity, IR, and dyslipidemia [123,128,129]. Women with polycystic ovaries (PCOs) have higher chances of developing CVDs than normal women [127,129]. Existence research reports a greater preponderance of developing atherosclerotic conditions in women suffering from hirsutism, and evidence of substantial intima-media thickness has been recorded among affected patients [130,131]. Independent of facts like age, BMI, T2DM, and dyslipidemia, the study suggests that women with PCOS had 40% higher chances of getting hypertension than the non-PCOS women [132]. Evidence further indicated that the occurrence of pregnancy-associated hypertension (pre-eclampsia) was significantly greater in PCOS-affected patients [133,134].

Diabetes Mellitus and Gestational Diabetes

Along with obesity and T2DM, gestational diabetes mellitus (GDM) is on the rise, impacting an estimated 14% of births worldwide [135]. The disease's incidence varies according to variations in risk factors and screening and diagnostic procedures [136]. Furthermore, data indicated that from 2016 to 2021, there was a shift from 6.0% to 8.3% in the proportion of mothers who were diagnosed with GDM [135]. This condition arises from an imbalance in β-cell thresholds and their inability to meet insulin needs due to decreased sensitivity during pregnancy [136,137]. PCOS-affected patients often share the same metabolic abnormalities with women suffering from GDM [138,139]. GDM cases have witnessed high incidences of polycystic ovaries, irregular menstruation, and hirsutism, as compared to patients who have had uncomplicated pregnancies [140,141]. Both retrospective and

 doi:10.20944/preprints202412.2399.v1

prospective data exist to support the higher chances of GDM in PCOS patients [142,143], particularly if there is a history of hyperinsulinemia from premature conception [144].

Cancer

Extensive research has been conducted to provide evidence in favor of the hypothesis that obesity makes significant contributions to the evolution of cancer in endometrial cells [145,146]. T2DM has been shown to raise the incidence of endometrial cancer by as much as threefold, according to meta-analysis evidence [147,148]. There is a direct correlation between the elevated levels of estrogen that are linked with PCOS and the undeniable risk of developing endometrial cancer [149,150]. This is also reported from a meta-analysis that increased BMI is directly related to the risk of cancer [151]. Furthermore, evidence suggests that hormonal irregularities, particularly estrogens, may contribute to the initiation and progression of ovarian cancer [152]. A population-based study reported a high risk of ovarian cancer among PCOS patients having irregular menstrual cycles for long periods of time [153].

5. Criteria for Diagnosis

The National Institute of Child Health and Human Development endorsed the below-mentioned criteria based on three physical/physiological conditions. 1. Absence/irregular ovulation, resulting in menstrual irregularities such as light or missed periods. 2. High levels of androgens not due to other conditions or augmented body or facial hair. 3. Undergrowth of one or both of the ovaries, clumps of ovarian follicles as detected by ultrasound. A diagnostic approach requires either only features 1 and 2, or any two of the three for a PCOS diagnosis [154]. Then, "Rotterdam Criteria" expanded the PCOS phenotype to encompass any two of the three essential characteristics: oligo-amenorrhea, hyperandrogenism, and polycystic-appearing ovarian morphology on ultrasonography. With passing time and based on evidence, Androgen Excess Society (AES) declared hirsutism, biochemical hyperandrogenism, oligo-anovulation, and polycystic-appearing ovarian morphology (PCOM) to diagnose PCOS [121]. The major three diagnostic criteria have been depicted in **Figure 5**.

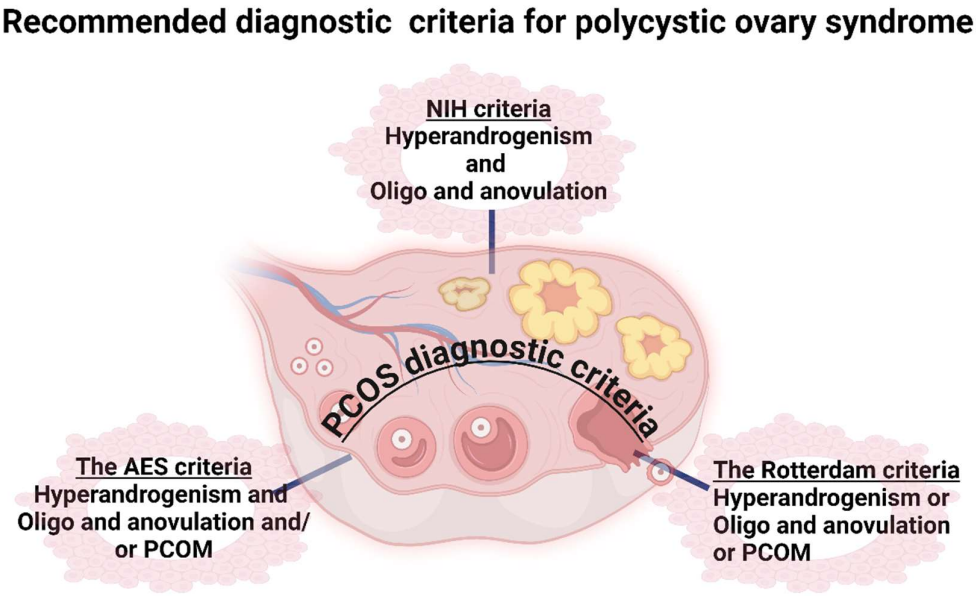

Figure 5.

 doi:10.20944/preprints202412.2399.v1

In 2012, the NIH held an evidence-based methodology workshop on PCOS, and experts further recommended broader use of 2003 modified Rotterdam criteria: (1) androgen excess and ovulatory dysfunction, (2) androgen excess and polycystic appearing ovarian morphology (PCOM), (3) ovulatory dysfunction and PCOM, and (4) androgen excess, ovulatory dysfunction, and PCOM [155]. The Rotterdam criteria (developed by the European Society for Human Reproduction and Embryology-ESHRE and the American Society for Reproductive Medicine-ASRM) are still the most extensively used as in the 2018, International Evidence-Based Guideline for the Assessment and Management of PCOS unanimously endorsed them [156]. Currently, It is recommended to use the modified Rotterdam criteria (discussed above) Focusing the PCOM, In 2014, the Androgen Excess and Polycystic Ovary Syndrome Society conducted a meta-analysis that supported raising the bar for polycystic ovarian morphology to at least 25 follicles, and they discovered that reproductive-aged women typically have a median FNPO ranging from 13 to 16 follicles [157].

6. Management of PCOS

PCOS management needs to address the conditions of hyperinsulinemia and hyperandrogenemia, both of which constitute the characteristic markers of PCOS disorder and are extensively addressed in the majority of the treatment strategies. Treatment strategies include changes in lifestyle to intervening pharmacological therapy. A decision support system for early diagnosis can significantly help in preventing or delaying the occurrence of PCOS [158]. The evidences for the management of PCOS has been summarized in Table 1.

Lifestyle Modifications

High BMI makes PCOS cases undergo different clinical and biochemical changes that even worse by exacerbating the reproductive and metabolic implications among PCOS patients [109,110]. Furthermore, it has a significant impact on the patient's outcome undergoing management of infertility, metabolic abnormalities, and menstrual dysfunction [112,159]. A decrease in body mass of up to just 5–10% is able to considerably improve the function of the ovaries and normalize the concentration of androgen in individuals who are afflicted by PCOS [159–161]. For the purpose of weight loss treatment, dietitians suggested incorporating a diet including a low carbohydrate content, more fiber content, and a low fat content into the consumption plan [12]. Diets rich in polyunsaturated fatty acids (PUFA), Vitamin D3, Vitamin E, and omega-3 fatty acids have been shown to modify the amount of glucose in the blood as well as sex hormones [162–164].

Pharmacological Interventions

Current management and drug therapy have been considered comparatively operative in PCOS, and still some cases go untreated despite different available interventions. A combination therapy of estrogen-progestin or individual progestin is opted as a primary option for treating oligomenorrhea or amenorrhea in case infertility is not the primary concern. Oral contraceptives (OCs) function by regulating menstruation, thus lowering the chances of developing hyperplasia in the endometrial tissue. Drugs that increase sensitivity to insulin still have a controversial contribution to the therapy to aid in ovulation. Moreover, surgery of the ovary and gonadotropin therapy are the available alternatives in the event of the failure of pharmacological therapy [165,166].

Antiandrogens

HA are routinely reported in the PCOS population owing to the accentuated concentrations of unbound testosterone. Oral contraceptives (OCs) are commonly considered the primary option in the pharmacological management of hirsutism and acne and not suitable for targeted PCOS treatment [167,168]. Moreover, there is a correlation between prescribing the anti-androgen medication at an earlier stage and an improved spontaneous fertility rate [169]. The efficacy of other OCPs for hirsutism was comparable to or hardly different from that of OCPs containing levonorgestrel,

 doi:10.20944/preprints202412.2399.v1

cyproterone acetate, or drospirenone. Finasteride and spironolactone are the drugs employed in the treatment of hirsutsmic conditions [170]. Eflornithine is the topical application used for managing hirsutism that affects the face and visible body parts [171,172]. Electrolysis or laser treatments along with eflornithine are favorably used to treat hirsute women, as waxing or shavings are means of temporary relief from the problem [173].

Antidiabetic Agents

Metformin and thiazolidinediones (TZDs) are frequently prescribed for the treatment of hyperinsulinemia; however, TZDs have little additional benefit [174–176]. Metformin is used to improve ovulation rates, normalize the BMI, and diminish the levels of testosterone as well as fasting insulin [176,177]. It is a well-established fact that altered glucose metabolism and hyperinsulinemia due to IR are much greater in PCOS patients. This evidence favors the metformin intervention to manifest improvement in the condition of polycystic ovaries, induce regularity in menstruation, and potentiate ovulation in all patients exhibiting anovulation, irrespective of their resistance to clomiphene citrate treatment [174–177]). Apart from certain undesirable outcomes like gastrointestinal symptoms, metformin, when administered in combination with a hypocaloric diet, showed more beneficial than weight management therapy [174]. Finally, it was concluded by yet another study that therapy with this agent could be concluded as an economical, safer, and easy alternative when compared to others even during in vitro fertilization [178,179]. Collective data on conception rate showed significant improvements in the combined group rather than the individual therapy. However, numerous meta-analyses showed that metformin and clomiphene citrate together were mainly relevant for clomiphene-resistant women with polycystic ovaries. [180,181]. Furthermore, during rFSH therapy, metformin has no discernible impact on ovarian response; however, it may restore ovulation in clomiphene citrate-resistant polycystic ovary syndrome patients with normal glucose tolerance, even if it does not improve insulin resistance. [180,182]. TZDs, namely rosiglitazone and pioglitazone, are employed to treat T2DM and possess an unbeatable impact on the ovaries by diminishing the secretion of estradiol and testosterone [138,176,177,183]. Some changes to the lifestyle must be inculcated, along with the administration of insulin sensitizers, for weight loss and improved BMI along with managing endocrine and metabolic abnormalities. This definitely ameliorates the fertility and ovulation among PCOS patients [159,161,179]. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two examples of incretin hormones that are well-known stimulators of glucose-dependent insulin release. GLP-1 agonists including liraglutide, semaglutide, dulaglutide, and exenatide, offer enhanced insulin sensitivity via reducing inflammation, free radical generation, and fatty acid metabolism. It also acts through increased expression and translation of GLUT-4, ameliorating endoplasmic reticulum (ER), and insulin signaling as evidenced [184,185]. The data from systematic review and meta-analysis reported that both GLP-1 and GIP receptor agonists are promising novel medicines that have the potential for managing PCOS conditions through various aspects [186–188]. Therefore, if they are shown to be useful in clinical research, they have the potential to be innovative therapy choices for women who have PCOS in order to improve metabolic risk.

Oral Contraceptives

Ovulation inducers, particularly tamoxifen, bromocriptine, clomiphene, gonadotropins, and GnRH, are drugs commonly employed to induce ovulation [189]. Aromatase inhibitors may yield an additional option of hormone therapy to treat PCOS patients [190]. Meantime, egg quality and egg quantity should be taken into consideration for evaluation by an endocrinologist before prescribing the patient with ovulation induction therapy. The age of the patient also plays a role in estimating the quality and quantity of eggs; for instance, both get compromised with age [191,192].

Clomiphene Citrate

 doi:10.20944/preprints202412.2399.v1

Clomiphene citrate (CC) has been widely employed for potentiating ovulation in women suffering from anovulation accompanied by infertility issues [193,194]. Its treatment in affected patients has claimed to achieve a 60–85% rate of ovulation and 30–40% chances of conception [195,196]. However, a 13-25% rate of abortion has also been reported [197]. It centrally potentiates the agonistic impact on the binding site, dampening their inhibitory effect, and accentuates the recurrence of pulsating gonadotropins, leading to ovulation [198]. CC is preferred because it is economical, has higher patient acceptability, seldom has fewer side effects, and aids in the spontaneous induction of growth in the follicles. Evidence suggests efficacy of CC in encouraging ovulation in PCOS subjects [199]. Approximately 50% of individuals who ovulate do so at a dose of 50 milligrams, another 20%–25% at a dose of 100 milligrams, and 10% at a dose of 150 milligrams. The absence of the ovulation process for up to three or four cycles of the treatment phase, even after administering the highest dose, is an indicator of drug resistance that can be treated with combination therapy.

Gonadotropins

Normal maturation, libido, and procreation depend on the gonadotropins, a family of peptide hormones that control ovarian and testicular function. FSH, LH, and human chorionic gonadotropin (HCG) are all human gonadotropins. The pituitary gland produces FSH and LH, whereas the placenta synthesizes the HCG. The majority of women who suffer from PCOS have abnormal gonadotropin production, particularly an elevated level of mean LH. Once the patient has been determined to be "clomiphene citrate-resistant," gonadotropins are traditionally prescribed in these cases [166,200]. Evidence for ovarian hyperstimulation and chances of multiple pregnancies, specifically in women already suffering from PCOS, is contraindicated in its use [200]. Moreover, for PCOS women who have tried and failed with CC, then FSH is a good alternative therapeutic option. To achieve optimum follicular development with fewer injections, molecular engineering has made possible to alter FSH preparations to extend their half-lives and therapeutic effects [201]. In women with PCOS who have not yet tried gonadotropin treatment, evidence indicates that it may be more beneficial than CC. Human menopausal gonadotropin (HMG), urinary FSH (uFSH), highly purified uFSH, recombinant FSH (rFSH), follitropin alpha, and follitropin beta are the gonadotropins used for ovulation induction in PCOS patients [200]. These analogues have already shown promise in assisted reproductive therapy.

Aromatase Inhibitors

Aromatase is an estrogen synthetase that potentiates production of estradiol and estrone by facilitating the conversion of testosterone and androstenedione. The disparity in ovulation and pregnancy rates caused by CC due to antiestrogenic action on the endometrium and cervical mucus has suggested use of aromatase inhibitors (AIs) as a possible substitute for CC in inducing ovulation [202]. Letrozole, the most frequently utilized aromatase inhibitor for ovulation induction, is given in doses ranging from 2.5 to 7.5 mg per day for a duration of 5 days, commencing on days 3 to 7 of the menstrual cycle [203]. In the past ten years, numerous studies have been published regarding the use of Letrozole for inducing ovulation in women with PCOS. It is clearly demonstrated that letrozole is equally effective as CC in terms of ovulation rate, pregnancy rate, live birth rate, and rates of multiple pregnancies [190,204]. In summary, letrozole is not advisable as the primary pharmacological treatment for ovulation induction in patients with PCOS; however, it may serve as a more suitable option for specific individuals, particularly those who are obese or resistant to CC [205,206].

Laproscopic Ovarian Drilling

The emerging advances in techniques of laproscopy velocified this evolving surgical approach to address the problem of PCOS [207,208]. Laparoscopic ovarian drilling (LOD) involves 3–6 incisions made with an insulated needle positioned at a 45-degree angle to the ovarian surface, using unipolar

 doi:10.20944/preprints202412.2399.v1

current. This results in a local and systemic decrease in androgen and inhibin levels, thus elevating FSH levels, which facilitates follicular development and ovulation [201,209]. Recent research indicated that obesity, prolonged infertility over three years, low baseline LH levels below 10 IU/l, testosterone levels above 4.5 nmol/l, and elevated basal AMH levels above 7.7 ng/ml may correlate with a suboptimal response to LOD [211]. Despite its benefits, LOD is not the primary treatment for PCOS nor the preferred option for CC-resistant PCOS due to the emergence of various safe and effective oral alternatives and the broader acceptance of a relatively safe low-dose step-up regimen of gonadotropin therapy [212]. Indeed, LOD, both with and without medical ovulation induction, may reduce the live birth rate in women with anovulatory PCOS and CC resistance as compared to medical ovulation induction alone [213]. It is also obvious that letrozole and LOD both provide comparable efficacy in attaining live birth rates in individuals with CC-resistant PCOS. Consequently, knowing determinants of LOD success is crucial for enhancing outcomes and preventing needless surgery [211].

7. Other Pharmacological Interventions

Inositols

Inositol is a natural compound, and its related two compounds, myoinositol and d-chiro-inositol, are the most available isomers among their nine isomeric forms. This phosphatidyl-myoinositol precedes the synthesis of inositol triphosphate (InsP3) that functions as an intracellular signaling molecule and controls the activity of many endocrine secretions such as TSH, FSH, and insulin [214]. Activation of myoinositol-based secondary messengers enhances glucose uptake by upregulating glucose transport mechanisms. However, activation of d-chiro-inositol secondary messengers promotes glycogen synthesis. The alterations in the insulin signaling system may lead to insulin resistance by hindering insulin signaling cascades. Importantly, epimerase is an enzyme that transforms myoinositol into d-chiro-inositol while preserving a natural ratio of 40:1 for most tissues [215]. Myoinositol consumption has been shown to enhance ovulation and increase the effectiveness of reproductive therapies in PCOS women who are unable to conceive naturally [215,216]. Moreover, its treatment significantly decreased both the time required for ovulation induction and the amount of recombinant FSH needed [217]. Concurrent to increased insulin sensitivity, myoinositol treatment significantly reduces the levels of androstenedione, LH, LH/FSH ratio, prolactin, and insulin [218]. These improvements have substantial impacts on endocrine, metabolic, and reproductive parameters. However, both clinicians and patients should be engaged in shared decision-making about inositol for PCOS. It is important to take into account both the ambiguity of the evidence and individual beliefs and preferences. [219,220].

MicroRNA Therapy

The significant association among miRNAs, obesity, and dyslipidemia highlights the therapeutic possibility of targeting PCOS-related metabolic alterations [221]. Evidence suggests that miRNAs might serve as valuable clinical indicators for diagnosing PCOS and as a target for therapeutic interventions in the treatment of PCOS [222–224]. Based on miRNA profiling, it might enhance the provision of individualized medical treatment for PCOS. High-throughput sequencing and profiling of microRNAs may improve clinical management and help patients by choosing the most effective treatment for infertility. Through the use of cutting-edge technology and easily available databases, this instrument offers accurate diagnosis, prevention, and treatment of reproductive issues related to PCOS [35,225] Deswal and Dang, 2020). The main objective is to conduct comprehensive replication tests in order to identify particular miRNAs that have substantial modulatory effects on PCOS, and this will provide innovative possibilities and convincing alternatives for PCOS-associated metabolic problems. Therapeutics, including small interfering RNA (siRNA), anti-miRNA oligonucleotides, and miRNA mimics, are the current areas of scientific interest [44,226]. The miRNAs that have a role

 doi:10.20944/preprints202412.2399.v1

in PCOS are not yet the focus of any therapy. However, investigating miRNAs that are associated with PCOS may provide new opportunities for future research on PCOS [44,227,228].

Interleukin-22 Therapy

Interleukin-22 (IL-22) is a central mediator secreted by immune cells and reported to be responsible for inflammation, mucous production, microbial infection, tissue regeneration, and facilitating the body's defensive mechanisms. It does this by restraining cellular necrosis and tissue damage either due to inflammation or different infections, thus maintaining homeostasis for body immunity [229,230]. Metabolic abnormalities and immunological challenges associated with persistent low-grade inflammation are prevalent in persons with PCOS. Recent studies indicate that IL-22 is therapeutically helpful in addressing immunological dysfunction and metabolic disorders, implying its potential relevance in the treatment of PCOS. [231–233]. Another study showed that IL-22-associated browning of white adipose tissue plays a major role in regulating tissue sensitivity to insulin and ovarian functions in PCOS. This endorses the potential therapeutic application for treating PCOS with HA phenotype [234]. Exogenous IL-22 treatment has been shown to have therapeutic advantages, as evidenced by experimental studies. Decreased IL-22 may play a role in the onset of PCOS. IL-22 stimulates cell proliferation, prevents apoptosis, and controls steroidogenic human granulosa-like tumor cell line (KGN) cell steroidogenesis when exposed to lipopolysaccharide [235]. Concurrently, Geng and coworkers (2023) have reported that IL-22 could potentially serve as a viable therapeutic agent for PCOS patients in the future. Given the circumstances, the IL-22 pathway might open another door for intervention in diseases related to metabolic alterations like PCOS [232].

Restoration of the Gut Microbiome

The development of PCOS-related symptoms might be significantly influenced by an imbalance in the gut flora [236]. With enhanced comprehension and pathological involvements of gut microbiota, substantial efforts have been made to develop innovative approaches for managing PCOS [237,238]. Treatment options related to PCOS include probiotics (living microorganisms), prebiotics (sources of food for good gut bacteria), synbiotics, and more modern treatments such as fecal microbiota transplants [239,240]. In nature, probiotic bacteria grow in food post-fermentation and possess antioxidant, antimicrobial, and anti-inflammatory effects [241–243]. They also have the capacity to ameliorate metabolic parameters like IR and dyslipidemia, maintaining dysbiosis, and modifying the immune system [244]. The most important bacterial families related to probiotics include the Lactobacillus, Bifidobacterium, Lactococcus, Carnobacterium, Enterococcus, Streptococcus, Pediococcus, Propionibacterium, Leuconostoc, and Bacillus species, Saccharomyces yeasts, and Aspergillus molds [245]. Multiple mechanisms contribute to the development and worsening of PCOS, including dysbiosis in the gut microbiota, which significantly regulates HA, IR, chronic inflammation, and metabolic abnormalities [246]. Probiotics significantly impact the regulation of hormonal and inflammatory indicators, according to a new meta-analysis. The study indicated a major decrease in the HA and malondialdehyde, as well as an increase in SHBG and nitric oxide. Additionally, probiotics have been shown to improve weight, BMI, HOMA-IR, insulin levels, dyslipidemia, hirsutism, as well as total testosterone [246–248]. Prebiotics exert their effects in several ways, such as selectively stimulating the activity of beneficial bacteria in the intestines, undergoing fermentation by the gut microbiota, and inhibiting the colonization of pathogens by interacting with them. According to some research, prebiotics promote the proliferation of gut microbiota and indirectly promote the therapeutic benefits of probiotics [236,246–248]. Further research is necessary to clarify the efficacy of various prebiotics and probiotic strains and doses, establish the optimal treatment regimen, and demonstrate its beneficial impact on clinical outcomes in PCOS.

Fecal microbiota transplants (FMTs) are a cutting-edge biotherapy that entails transferring the fecal fluid from healthy individuals who have undergone intestinal treatment. The purpose is to rebuild the intestinal flora and effectively cure the ailments in question [249]. FMTs have emerged as an effective approach in the treatment of metabolic diseases [250,251]. FMTs can decrease intestine

 doi:10.20944/preprints202412.2399.v1

permeability by increasing short-chain fatty acid synthesis, promoting the intestinal adaptive immune response, and controlling gut microflora. They can also modulate blood sugar levels and insulin sensitivity and may influence inflammatory cytokine production [250,252]. In vivo research shows FMTs decrease testosterone levels, increase estrogen levels, and support menstrual cycle maintenance [253]. A new theory suggests altered gut microbiota in PCOS conditions and FMTs could be effective in treatment, reducing the remission rates in PCOS [248,254]. An analysis of publicly available data revealed that the microbial characteristics of PCOS patients, especially those with varying testosterone levels, establish a basis for further research into the pathogenesis of PCOS and the formulation of effective diagnostic, treatment, and intervention strategies [255].

Statins

Statins have been added as newer treatment options as they decrease the production of sex steroid and ovarian androgen by preventing androgen production in thecal cells [156–158]. New research lends credence to the idea that the mevalonate pathway is crucial to thecal interstitial cell function and that statin-induced alterations in this system may have a positive impact on PCOS and CVDs [258]. In another study, clinical and biochemical abnormalities, such as ovulation dysfunction, in women with PCOS have been shown to improve with long-term statin treatment [259]. Moreover, atorvastatin may induce a decrease in the levels of testosterone and other androgens by decreasing the level of cholesterol, which is the precursor of the steroidogenesis pathway. Testosterone and other androgens are essential for the proper functioning of the reproductive physiology. There is a possibility that atorvastatin may result in adverse effects in the majority of situations due to the potential reduction in androgen levels. Conversely, in the context of polycystic ovary syndrome (PCOS), the administration of atorvastatin may be advantageous for the reduction of excessive androgen levels [260]. The evidence also suggests the use of statins and adjunct therapy with first line drugs used in PCOS management, particularly those associated with dyslipedimia [81,261].

Vitamin D and Calcium Supplements

Evidence suggests that follicle maturation, HA, and menstrual regularity are all improved with vitamin D and calcium supplementation for PCOS [118,262]. Vitamin D modulates AMH signaling, FSH sensitivity, and progesterone levels in human granulosa cells, all of which are important for ovarian follicular growth [119]. Women who suffer from PCOS have aberrant ovarian folliculogenesis due to elevated AMH levels. An improvement in folliculogenesis may be directly connected to vitamin D treatment via a decrease in blood AMH levels [117]. For PCOS individuals who are vitamin D insufficient, taking the supplement improves insulin sensitivity as well. The systematic review and meta-analysis overviewed the impact of vitamin D supplementation on biomarkers of inflammation and oxidative stress in women with PCOS [263]. Numerous studies have shown that IR in PCOS is associated with vitamin D insufficiency and reported to have beneficial effects on insulin metabolism and the lipid profile of infertile women with PCOS who are candidates for IVF in particular [263,264].

Table 1. Management of polycystic ovary syndrome.

Category	Mechanism of action	Efficacy	Side effects	Dose/Duration	Reference
Lifestyle modifications	Lifestyle treatment (diet, exercise, behavioral or combined treatments)	Improved free androgen index, Weight reduction, Reduced body mass index, Improved OGTT	Not available	2-3sessions of 40 to 60 minutes per week of an aerobic training programme	[111,112,159,179]
OCs					

 doi:10.20944/preprints202412.2399.v1

Levonorgestrel	Binds to progesterone and androgen receptors and decreases the GnRH release from the hypothalamus	Menstrual cyclicity by inhibiting ovulation, Hirsutism, Acne	Nausea, Breast tenderness, Bleeding, weight gain, dark pigmentation of facial skin	30 µg/day	[161,167,175,265]
Ethinyl estradiol	Estrogen receptor (Erα or Erβ) agonist	Inhibiting the release of gonadotropins to prevent ovulation, altering the endometrial lining to prevent implantation, and modifying cervical mucus to inhibit sperm penetration	Headache or migraine, menstrual irregularities, nausea and vomiting, breast pain or tenderness, mood changes, fatigue, irritability, decreased libido, increased weight	20-30 µg/day for 28 days	[161,167,175,265–268]
Estradiol valerate			Headaches, irregular uterine bleeding, breast tenderness, nausea and vomiting, acne, and increased weight	5 mg per day for 5 days	[161,167,175,269]
Cyproterone acetate	Blocking androgen receptors	Suppresses LH Reduces testosterone level Inhibits ovulation	Dysmenorrhea, breast tenderness, change in libido, headache, depression, nervousness, chloasma, varicosity, edema, dizziness	2 mg per day	[161,167,175,265,267,268]
Drospirenone	Aldosterone receptors antagonist	High antigonadotropic activity Blockade of ovulation Prevention of follicular growth	PMS, headache or migraine, breast discomfort/tenderness, nausea and vomiting, abdominal discomfort, mood changes	3 mg per day for 28 days	[161,167,175,265,268,270]

 doi:10.20944/preprints202412.2399.v1

Dienogest	Progesterone receptor (PR) agonist	Progestogenic effect on the endometrium and inhibits the increase in the estradiol level through the inhibition of the growth of ovarian follicles. Inhibits ovulation	Headaches, irregular uterine bleeding, breast tenderness, nausea and vomiting, acne, and increased weight	2-4mg/day	[161,167,175,269,271]
Chlormadinone acetate			Breast pain or tension, depressed state, loss of libido, migraine or headache	2 mg per day	[161,167,175,269, 270,272]
Progestins					
Medroxyprogesterone acetate	Activates the progesterone receptor	Inhibits the production of gonadotropin, preventing follicular maturation and ovulation	Amenorrhea, change in menstrual flow, hot flash, weight gain or weight loss, menstrual disease, abdominal pain, headache, nervousness	8-10 mg per day	[161,167,175,273]
Antiandrogens					
Finasteride	Inhibitor of type II 5-alpha-reductase	Blocking androgens in the hair follicles, it lessens the PCOS-related hair loss	Risk for teratogenicity in male fetuses	0.5 to 55 mg per day. depending on patient condition (3-4 months)	[168,170,274]
Spironolactone	Competitive antagonistic activity against aldosterone receptors	Synergism with COCs	Nausea and menstrual irregularities Inhibition of adrenal and ovarian steroidogenesis	50 mg bid on days 5–25 of menstrual cycle (09 months)	[275,276]
Antiestrogens					
Clomiphene citrate	Blocks ERs, Inhibiting normal estrogen negative feedback, which results in increased pulsatile GnRH secretion from the	Increased pulsatile GnRH secretion from the hypothalamus. Secretion of FSH and LH. Follicle growth and maturations	Ovarian enlargement, flush, pelvic discomfort, breast discomfort, blurred vision, photophobia, diplopia, abnormal uterine bleeding intermenstrual spotting, menorrhagia	50-100 mg per day for 5 days	[180,194,198,204]

 doi:10.20944/preprints202412.2399.v1

	hypothalamus and pituitary gonadotropin release	Ovulation induction	Increased bone or tumor pain, or reddening around the tumor site.		
Tamoxifen			Hot flashes, nausea. Excessive tiredness, dizziness, depression, headache	60 mg/day PO 5 days	[277,278]
Aromatase inhibitors					
Letrozole	Competitive inhibitor of the aromatase enzyme.	Prevents conversion of androgens to estrogens Ovulation induction	Hot flashes, arthralgia, flushing, asthenia, edema, arthralgia, headache, dizziness, hypercholesterolemia, sweating increased, bone pain	2.5 to 7.5 mg for 5 days	[190,203,279]
Laparoscopic ovarian drilling	Surgical intervention	Ameliorating disturbances of the ovarian-pituitary feedback mechanism Promote follicular recruitment, maturation and subsequent ovulation.	Bleeding, Infection, Adhesions or scarring of ovary	None	[190,208,211,213]
Gonadotrophins					
Human menopausal gonadotropins (HMG)	Stimulate LH and FSH activity	promotes follicle maturation, stimulate ovulation and corpus luteum development.	Pain at the injection site, skin erythema, muscle pain	75-150 U per day for 2 weeks	[280,281]
Urinary FSH (uFSH)	FSH specific activity LH activity- - (<2%-5%)	Stimulates ovary Follicle growth and maturations	Pain at injection sites Enlarged ovaries	35-40 IU per day	[282–284]

 doi:10.20944/preprints202412.2399.v1

recombinant FSH (rFSH) -99% purity	FSH specific activity LH activity-None	Ovulation induction	Abdominal swelling and discomfort Nausea or even vomiting	75-225 IU per day	[182,282,283]
Follitropin alpha (Human FSH rDNA preparation)	Similar to FSH activity			Initial dose of first cycle: 75 IU SC qDay; Dose can be increased based on response	[280,281,285]
Follitropin beta (Human FSH rDNA preparation)				150-225 units SC/IM for at least 4 days Dose can be increased based on response	[280,281,286]
Antidiabetic agents					
Metformin	Decreased glucose production (hepatic) and its intestinal absorption, Improved insulin sensitivity	Antidiabetic agent for type II diabetes weight loss and has a lesser effect on lowering Testosterone levels. It improves ovulation and decreases androgen levels. Reduces insulin level increases insulin sensitivity.	Diarrhea, nausea and vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache	1500–2550 mg/day (500 1500–2550 mg/day03 months	[138,174,175,179]
Rosiglitazone	PPARγ-Agonist	Reduces BG level Increased insulin sensitivity Balances plasma lipid levels	Allergic reactions, Headache Chest pain (angina)	4 mg/day 06 months	[287–289]
Pioglitazones	PPARγ-Agonist	Reduces BG level	URTIs, Headache, Myalgia,	15-30 mg PO with meal qDay	[183,290]

 doi:10.20944/preprints202412.2399.v1

		Increased insulin sensitivity			
Troglitazones	PPARγ-Agonist	Reduces BG level Increased insulin sensitivity Greater effects on testosterone levels	URTIs, Headache. UTIs. Diarrhea, Malaise Inflammation in extremities	200-400 mg OD	[289,291]
Empagliflozin	SGLT-2 inhibitor	Glucose reabsorption from the PCT Lowers renal glucose threshold Reduces PCOS related comorbidities	Urinary tract infections Female genital mycotic infections	10 mg OD	[292–294]
Dapagliflozin			Thrush, Back pain, Urinary tract infections female genital mycotic infections	5 mg OD	[295]
Sitagliptin	DPP-4 inhibitor	Improves Incretin levels, Increases insulin synthesis	Upper respiratory tract infection, nasopharyngitis, headache	100 mg OD	[296–298]
Liraglutide	GLP-1 receptor agonist	Improved glucose-dependent insulin secretion and maintains glucagon secretion Reduces gastric emptying and food intake	Tachycardia, Hypoglycemia, GI disturbances	0.6 mg to 3 mg OD	[299,300]
Semaglutide			GI disturbances	Oral dose: 7 to 14 mg orally OD. S.C. dose: 0.25 mg once a week for 4 weeks, then 0.5 mg once a week	[301]
Exenatide			Hypoglycemia, GI disturbances	5-10 mcg S.C. twice daily	[184,185]
Statins					
Rosuvastatin	3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase) inhibitor	Reduces HMG-CoA And cholesterol biosynthesis	Nasopharyngitis, arthralgia	20 mg OD	[256,258,302]
Atorvastatin			Diarrhea, pain in extremity	20 mg OD	[258,303]
Simvastatin			Upper respiratory infections headache abdominal pain constipation	20 mg OD	[81,258,260,261]

 doi:10.20944/preprints202412.2399.v1

			nausea		
Others					
Inositol	Second messengers of the insulin-signaling pathway synthesis.	Insulin-sensitizing and mimetic effects, lowering blood glucose and promoting hepatic glycogen	Not well-evidenced	1000-4000 mg per day 12-24 weeks	[214,218–220]
miRNA therapy (small interfering RNA (siRNA), anti-miRNA oligonucleotides, miRNA mimics	Downstream target of AR - miRNA	Downstream target of AR miR-200b, which is required for HPO axis-mediated ovulation. MiR-29c acts through the downstream pathways that affect androgen receptor localization.	Inefficient delivery Immune mediated toxicities	Not applicable	[36,44,229]
Interleukin-22 (IL-22) therapy	Binds to IL-22 receptor complex (IL-22R) Activating the IL-22R downstream signalling pathway	Stimulates cell proliferation, prevents apoptosis, and controls steroidogenic human granulosa-like tumor cell line (KGN) cell steroidogenesis when exposed to lipopolysaccharide	Body inflammation, osteoporosis, diabetes, and vulnerability to infection	Variable	[87,231,232,234,304,305]
Gut microbiota (Probiotics, prebiotics, and synbiotics FMTs	Maintenance of metabolic homeostasis	Antioxidant, antimicrobial, and anti-inflammatory effects Modifying the immune system Regulates HA	Not available	Variable	[237,238,248]
Vitamin D	Modulation of AMH signaling, FSH sensitivity,	Follicle maturation, HA, and menstrual regularity	Not reported at normal dose supplement	50,000 IU of Vitamin D every other week for 8 weeks	[117–119,262]

 doi:10.20944/preprints202412.2399.v1

	and progesterone levels

PCOS: Polycystic ovary syndrome, OGTT: Oral glucose tolerance test, LH: Luteinizing hormone; COCs: Combined oral contraceptive pill, GnRH: Gonadotropin-releasing hormone, FSH: Follicle stimulating hormone, IU: international unit, S.C.: Subcutaneous injection, I.M.: Intramuscular Injection, BG: Blood glucose, PCT: Proximal convoluted tubule, OD: Once a day, HA: Hyperandrogenism, FMTs: Faecal microbiota transplantation, AMH: Anti-mullerian hormone, HPO: Hypothalamic-pituitary-ovarian, miR/miRNA: Micro ribonucleic acid, AR: androgen receptor.

9. Future Perspectives

Clinically speaking, PCOS is a complicated ailment that may cause issues throughout a woman's lifetime. Furthermore, it is becoming an increasingly common feminine disorder among the reproductive age group population. This disease presents a number of challenges, in particular inaccurate diagnostic criteria and the tremendous variations and complications of its characteristic features. Realtime deployment of tailored therapeutic techniques will improve the overall PCOS and thus comorbidities and better HRQOL. Early identification and treatment are vital in order to enhance the prognosis among females who may encounter infertility throughout their reproductive years. There is a possibility that key gene polymorphisms for screening of PCOS subtypes might be supportive in the early PCOS identification. For the purpose of determining effective preventative methods as well as treatment approaches, it will be important to explore more research on PCOS-associated genetic alterations. As supplementation with prebiotics, probiotics, and synbiotics in women who have PCOS seems to enhance a number of biochemical results and have positive benefits, it is necessary to do more studies in order to determine whether or not the composition of intestinal bacteria changes PCOS conditions. Thorough and practical research in the future will pave the way for the gut microbiota to be used as a PCOS biomarker. Additionally, the targeted and individualized alteration of the gut microbiota will contribute to the advancement of this study. There is a need for more study to evaluate the importance of the above-discussed drugs in the management of PCOS, or maybe in the prevention of its characteristic features. Therapies, up to this point, focused on alleviating symptoms rather than treating the sickness itself, and there is no cure for the condition. It is imperative that extensive efforts be made to conduct a comprehensive investigation of the illness in order to enhance treatment and postpone the severe long-term effects that the sickness has on the PCOS patients. There are a number of new chemical entities under study for managing T2DM that can be explored for implications in managing metabolic complications of PCOS. However, clinical trials are required to assess the clinical effectiveness and safety of these therapies in women who have PCOS. In order to show that novel medicines, such as miRNA therapy, IL-22 therapy, and others, have the ability to successfully treat PCOS, it will be important to do more study.

10. Conclusion

PCOS patients continue to struggle with a significant issue that has a negative impact on their HRQOL. It has been stated that several clinical elements may be used to correct the principal clinical and biochemical indications of PCOS, despite the fact that there are variations in the clinical presentation of PCOS among young women. When considering the possibility of becoming pregnant, it is necessary to implement appropriate lifestyle management and therapeutic intervention, the specifics of which are determined by the severity of the comorbid disease and the clinical signs. Furthermore, a strategy that is founded on research needs to be adapted to the specific needs of each individual woman.

Funding: Deanship of Research and Graduate Studies, King Khalid University (Grant number RGP2/317/45).

 doi:10.20944/preprints202412.2399.v1

Acknowledgements: "The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through Large Research Project under grant number RGP2/317/45 "

Conflict of Interest: The authors declare no conflicts of interest.

References

1. World health organisation Polycystic Ovary Syndrome Available online: https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome (accessed on 25 December 2024).
2. Louwers, Y.V.; Laven, J.S.E. Characteristics of Polycystic Ovary Syndrome throughout Life. Ther. Adv. Reprod. Health 2020, 14, 2633494120911038, doi:10.1177/2633494120911038.
3. Islam, H.; Masud, J.; Islam, Y.N.; Haque, F.K.M. An Update on Polycystic Ovary Syndrome: A Review of the Current State of Knowledge in Diagnosis, Genetic Etiology, and Emerging Treatment Options. Womens. Health (Lond.Engl.) 2022, 18, 17455057221117966, doi:10.1177/17455057221117966.
4. Witchel, S.F.; Oberfield, S.E.; Peña, A.S. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment with Emphasis on Adolescent Girls. J. Endocr. Soc. 2019, 3, 1545–1573, doi:10.1210/js.2019-00078.
5. Kiconco, S.; Teede, H.J.; Azziz, R.; Norman, R.J.; Joham, A.E. The Need to Reassess the Diagnosis of Polycystic Ovary Syndrome (PCOS): A Review of Diagnostic Recommendations from the International Evidence-Based Guideline for the Assessment and Management of PCOS. Semin. Reprod. Med. 2021, 39, 71–77, doi:10.1055/s-0041-1735259.
6. Tay, C.T.; Mousa, A.; Vyas, A.; Pattuwage, L.; Tehrani, F.R.; Teede, H. 2023 International Evidence-Based Polycystic Ovary Syndrome Guideline Update: Insights from a Systematic Review and Meta-Analysis on Elevated Clinical Cardiovascular Disease in Polycystic Ovary Syndrome. J. Am. Heart Assoc. 2024, 13, e033572, doi:10.1161/JAHA.123.033572.
7. Ganie, M.A.; Vasudevan, V.; Wani, I.A.; Baba, M.S.; Arif, T.; Rashid, A. Epidemiology, Pathogenesis, Genetics & Management of Polycystic Ovary Syndrome in India. Indian J. Med. Res. 2019, 150, 333–344, doi:10.4103/ijmr.IJMR_1937_17.
8. Glueck, C.J.; Goldenberg, N. Characteristics of Obesity in Polycystic Ovary Syndrome: Etiology, Treatment, and Genetics. Metabolism 2019, 92, 108–120, doi:10.1016/j.metabol.2018.11.002.
9. Qu, X.; Donnelly, R. Sex Hormone-Binding Globulin (SHBG) as an Early Biomarker and Therapeutic Target in Polycystic Ovary Syndrome. Int. J. Mol. Sci. 2020, 21, 8191, doi:10.3390/ijms21218191.
10. Huang, R.; Wang, Y.; Yan, R.; Ding, B.; Ma, J. Sex Hormone Binding Globulin Is an Independent Predictor for Insulin Resistance in Male Patients with Newly Diagnosed Type 2 Diabetes Mellitus. Diabetes Ther. 2023, 14, 1627–1637, doi:10.1007/s13300-023-01445-x.
11. Wallace, I.R.; McKinley, M.C.; Bell, P.M.; Hunter, S.J. Sex Hormone Binding Globulin and Insulin Resistance. Clin. Endocrinol. (Oxf.) 2013, 78, 321–329, doi:10.1111/cen.12086.
12. Kite, C.; Lahart, I.M.; Afzal, I.; Broom, D.R.; Randeva, H.; Kyrou, I.; Brown, J.E. Exercise, or Exercise and Diet for the Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Syst. Rev. 2019, 8, 51, doi:10.1186/s13643-019-0962-3.
13. Kanbour, S.A.; Dobs, A.S. Hyperandrogenism in Women with Polycystic Ovarian Syndrome: Pathophysiology and Controversies. Androg. Clin. Res. Ther. 2022, 3, 22–30, doi:10.1089/andro.2021.0020.
14. Rosenfield, R.L.; Ehrmann, D.A. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr. Rev. 2016, 37, 467–520, doi:10.1210/er.2015-1104.
15. Moursi, M.O.; Salem, H.; Ibrahim, A.R.; Marzouk, S.; Al-Meraghi, S.; Al-Ajmi, M.; Al-Naimi, A.; Alansari, L. The Role of Anti-Mullerian Hormone and Other Correlates in Patients with Polycystic Ovary Syndrome. Gynecol. Endocrinol. 2023, 39, 2247098, doi:10.1080/09513590.2023.2247098.
16. Mazerbourg, S.; Monget, P. Insulin-like Growth Factor Binding Proteins and IGFBP Proteases: A Dynamic System Regulating the Ovarian Folliculogenesis. Front. Endocrinol. (Lausanne) 2018, 9, 134, doi:10.3389/fendo.2018.00134.
17. Ruddenklau, A.; Campbell, R.E. Neuroendocrine Impairments of Polycystic Ovary Syndrome. Endocrinology 2019, 160, 2230–2242, doi:10.1210/en.2019-00428.

18. Moore, A.M.; Prescott, M.; Marshall, C.J.; Yip, S.H.; Campbell, R.E. Enhancement of a Robust Arcuate GABAergic Input to Gonadotropin-Releasing Hormone Neurons in a Model of Polycystic Ovarian Syndrome. Proc. Natl. Acad. Sci. U. S. A. 2015, 112, 596–601, doi:10.1073/pnas.1415038112.
19. Sanchez-Garrido, M.A.; Tena-Sempere, M. Metabolic Dysfunction in Polycystic Ovary Syndrome: Pathogenic Role of Androgen Excess and Potential Therapeutic Strategies. Mol. Metab. 2020, 35, 100937, doi:10.1016/j.molmet.2020.01.001.
20. Escobar-Morreale, H.F. Polycystic Ovary Syndrome: Definition, Aetiology, Diagnosis and Treatment. Nat. Rev. Endocrinol. 2018, 14, 270–284, doi:10.1038/nrendo.2018.24.
21. Bongrani, A.; Mellouk, N.; Rame, C.; Cornuau, M.; Guérif, F.; Froment, P.; Dupont, J. Ovarian Expression of Adipokines in Polycystic Ovary Syndrome: A Role for Chemerin, Omentin, and Apelin in Follicular Growth Arrest and Ovulatory Dysfunction? Int. J. Mol. Sci. 2019, 20, 3778, doi:10.3390/ijms20153778.
22. Lonardo, M.S.; Cacciapuoti, N.; Guida, B.; Di Lorenzo, M.; Chiurazzi, M.; Damiano, S.; Menale, C. Hypothalamic-Ovarian Axis and Adiposity Relationship in Polycystic Ovary Syndrome: Physiopathology and Therapeutic Options for the Management of Metabolic and Inflammatory Aspects. Curr. Obes. Rep. 2024, 13, 51–70, doi:10.1007/s13679-023-00531-2.
23. Gołyszny, M.; Obuchowicz, E.; Zieliński, M. Neuropeptides as Regulators of the Hypothalamus-Pituitary-Gonadal (HPG) Axis Activity and Their Putative Roles in Stress-Induced Fertility Disorders. Neuropeptides 2022, 91, 102216, doi:10.1016/j.npep.2021.102216.
24. Chaudhari, N.; Dawalbhakta, M.; Nampoothiri, L. GnRH Dysregulation in Polycystic Ovarian Syndrome (PCOS) Is a Manifestation of an Altered Neurotransmitter Profile. Reprod. Biol. Endocrinol. 2018, 16, doi:10.1186/s12958-018-0354-x.
25. Liao, B.; Qiao, J.; Pang, Y. Central Regulation of PCOS: Abnormal Neuronal-Reproductive-Metabolic Circuits in PCOS Pathophysiology. Front. Endocrinol. (Lausanne) 2021, 12, 667422, doi:10.3389/fendo.2021.667422.
26. Kawwass, J.F.; Sanders, K.M.; Loucks, T.L.; Rohan, L.C.; Berga, S.L. Increased Cerebrospinal Fluid Levels of GABA, Testosterone and Estradiol in Women with Polycystic Ovary Syndrome. Hum. Reprod. 2017, 32, 1450–1456, doi:10.1093/humrep/dex086.
27. Watanabe, M.; Fukuda, A.; Nabekura, J. The Role of GABA in the Regulation of GnRH Neurons. Front. Neurosci. 2014, 8, 387, doi:10.3389/fnins.2014.00387.
28. Veldhuis, J.D. The Hypothalamic Pulse Generator: The Reproductive Core. Clin. Obstet. Gynecol. 1990, 33, 538–550, doi:10.1097/00003081-199009000-00021.
29. Pérez-López, F.R.; Ornat, L.; López-Baena, M.T.; Santabárbara, J.; Savirón-Cornudella, R.; Pérez-Roncero, G.R. Circulating Kisspeptin and Anti-Müllerian Hormone Levels, and Insulin Resistance in Women with Polycystic Ovary Syndrome: A Systematic Review, Meta-Analysis, and Meta-Regression. Eur. J. Obstet. Gynecol. Reprod. Biol. 2021, 260, 85–98, doi:10.1016/j.ejogrb.2021.03.007.
30. Liu, J.; Qu, T.; Li, Z.; Yu, L.; Zhang, S.; Yuan, D.; Wu, H. Serum Kisspeptin Levels in Polycystic Ovary Syndrome: A Meta-Analysis. J. Obstet. Gynaecol. Res. 2021, 47, 2157–2165, doi:10.1111/jog.14767.
31. Hestiantoro, A.; Noor Al Maghfira, R.; Fathmasari, R.; Rahmala Febri, R.; Ongko Joyo, E.; Muharam, R.; Pratama, G.; Bowolaksono, A. Altered Expression of Kisspeptin, Dynorphin, and Related Neuropeptides in Polycystic Ovary Syndrome: A Cross-Sectional Study. Int. J. Reprod. Biomed. (Yazd) 2024, 22, 395–404, doi:10.18502/ijrm.v22i5.16440.
32. Abdalla, M.A.; Shah, N.; Deshmukh, H.; Sahebkar, A.; Östlundh, L.; Al-Rifai, R.H.; Atkin, S.L.; Sathyapalan, T. Impact of Pharmacological Interventions on Biochemical Hyperandrogenemia in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Arch. Gynecol. Obstet. 2023, 307, 1347–1376, doi:10.1007/s00404-022-06549-6.
33. Abbara, A.; Clarke, S.A.; Dhillo, W.S. Clinical Potential of Kisspeptin in Reproductive Health. Trends Mol. Med. 2021, 27, 807–823, doi:10.1016/j.molmed.2021.05.008.
34. Hu, K.-L.; Chen, Z.; Li, X.; Cai, E.; Yang, H.; Chen, Y.; Wang, C.; Ju, L.; Deng, W.; Mu, L. Advances in Clinical Applications of Kisspeptin-GnRH Pathway in Female Reproduction. Reprod. Biol. Endocrinol. 2022, 20, 81, doi:10.1186/s12958-022-00953-y.

35. Deswal, R.; Dang, A.S. Dissecting the Role of Micro-RNAs as a Diagnostic Marker for Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Fertil. Steril. 2020, 113, 661-669.e2, doi:10.1016/j.fertnstert.2019.11.001.
36. Luo, Y.; Cui, C.; Han, X.; Wang, Q.; Zhang, C. The Role of miRNAs in Polycystic Ovary Syndrome with Insulin Resistance. J. Assist. Reprod. Genet. 2021, 38, 289–304, doi:10.1007/s10815-020-02019-7.
37. Heidarzadehpilehrood, R.; Pirhoushiaran, M. Biomarker Potential of Competing Endogenous RNA Networks in Polycystic Ovary Syndrome (PCOS). Noncoding RNA Res. 2024, 9, 624–640, doi:10.1016/j.ncrna.2024.01.002.
38. O'Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front. Endocrinol. (Lausanne) 2018, 9, 402, doi:10.3389/fendo.2018.00402.
39. Solís-Toro, D.; Mosquera Escudero, M.; García-Perdomo, H.A. Association between Circulating microRNAs and the Metabolic Syndrome in Adult Populations: A Systematic Review. Diabetes Metab. Syndr. 2022, 16, 102376, doi:10.1016/j.dsx.2021.102376.
40. Das, S.; Mohamed, I.N.; Teoh, S.L.; Thevaraj, T.; Ku Ahmad Nasir, K.N.; Zawawi, A.; Salim, H.H.; Zhou, D.K. Micro-RNA and the Features of Metabolic Syndrome: A Narrative Review. Mini Rev. Med. Chem. 2020, 20, 626–635, doi:10.2174/1389557520666200122124445.
41. Heneghan, H.M.; Miller, N.; Kerin, M.J. Role of microRNAs in Obesity and the Metabolic Syndrome. Obes. Rev. 2010, 11, 354–361, doi:10.1111/j.1467-789X.2009.00659.x.
42. Shi, M.; Mu, Y.; Zhang, H.; Liu, M.; Wan, J.; Qin, X.; Li, C. MicroRNA-200 and microRNA-30 Family as Prognostic Molecular Signatures in Ovarian Cancer: A Meta-Analysis. Medicine (Baltimore) 2018, 97, e11505, doi:10.1097/md.0000000000011505.
43. Di Martino, M.T.; Arbitrio, M.; Caracciolo, D.; Cordua, A.; Cuomo, O.; Grillone, K.; Riillo, C.; Caridà, G.; Scionti, F.; Labanca, C.; et al. miR-221/222 as Biomarkers and Targets for Therapeutic Intervention on Cancer and Other Diseases: A Systematic Review. Mol. Ther. Nucleic Acids 2022, 27, 1191–1224, doi:10.1016/j.omtn.2022.02.005
44. Vitale, S.G.; Fulghesu, A.M.; Mikuš, M.; Watrowski, R.; D'Alterio, M.N.; Lin, L.-T.; Shah, M.; Reyes-Muñoz, E.; Sathyapalan, T.; Angioni, S. The Translational Role of miRNA in Polycystic Ovary Syndrome: From Bench to Bedside-A Systematic Literature Review. Biomedicines 2022, 10, 1816, doi:10.3390/biomedicines10081816.
45. Esteves, J.V.; Enguita, F.J.; Machado, U.F. MicroRNAs-Mediated Regulation of Skeletal Muscle GLUT4 Expression and Translocation in Insulin Resistance. J. Diabetes Res. 2017, 2017, 1–11, doi:10.1155/2017/7267910.
46. Xiang, Y.; Mao, L.; Zuo, M.-L.; Song, G.-L.; Tan, L.-M.; Yang, Z.-B. The Role of MicroRNAs in Hyperlipidemia: From Pathogenesis to Therapeutical Application. Mediators Inflamm. 2022, 2022, 3101900, doi:10.1155/2022/3101900.
47. Sedgeman, L.R.; Michell, D.L.; Vickers, K.C. Integrative Roles of microRNAs in Lipid Metabolism and Dyslipidemia. Curr. Opin. Lipidol. 2019, 30, 165–171, doi:10.1097/MOL.0000000000000603.
48. Gao, Y.; Zou, Y.; Wu, G.; Zheng, L. Oxidative Stress and Mitochondrial Dysfunction of Granulosa Cells in Polycystic Ovarian Syndrome. Front. Med. (Lausanne) 2023, 10, 1193749, doi:10.3389/fmed.2023.1193749.
49. Zeber-Lubecka, N.; Ciebiera, M.; Hennig, E.E. Polycystic Ovary Syndrome and Oxidative Stress-from Bench to Bedside. Int. J. Mol. Sci. 2023, 24, doi:10.3390/ijms241814126.
50. Filippou, P.; Homburg, R. Is Foetal Hyperexposure to Androgens a Cause of PCOS? Hum. Reprod. Update 2017, 23, 421–432, doi:10.1093/humupd/dmx013.
51. Puttabyatappa, M.; Cardoso, R.C.; Padmanabhan, V. Effect of Maternal PCOS and PCOS-like Phenotype on the Offspring's Health. Mol. Cell. Endocrinol. 2016, 435, 29–39, doi:10.1016/j.mce.2015.11.030.
52. Diamanti-Kandarakis, E.; Papalou, O.; Kandaraki, E. Endocrine-Disrupting Chemicals and PCOS: A Novel Contributor in the Etiology of the Syndrome. In Polycystic Ovary Syndrome; Elsevier, 2022; pp. 227–244.
53. Peralta, M.; Lizcano, F. Endocrine Disruptors and Metabolic Changes: Impact on Puberty Control. Endocr. Pract. 2024, 30, 384–397, doi:10.1016/j.eprac.2024.01.006.

54. Pivonello, C.; Muscogiuri, G.; Nardone, A.; Garifalos, F.; Provvisiero, D.P.; Verde, N.; de Angelis, C.; Conforti, A.; Piscopo, M.; Auriemma, R.S.; et al. Bisphenol A: An Emerging Threat to Female Fertility. Reprod. Biol. Endocrinol. 2020, 18, 22, doi:10.1186/s12958-019-0558-8.
55. Srnovršnik, T.; Virant-Klun, I.; Pinter, B. Polycystic Ovary Syndrome and Endocrine Disruptors (Bisphenols, Parabens, and Triclosan)-A Systematic Review. Life (Basel) 2023, 13, 138, doi:10.3390/life13010138.
56. Zhang, X.; Chang, H.; Wiseman, S.; He, Y.; Higley, E.; Jones, P.; Wong, C.K.C.; Al-Khedhairy, A.; Giesy, J.P.; Hecker, M. Bisphenol A Disrupts Steroidogenesis in Human H295R Cells. Toxicol. Sci. 2011, 121, 320–327, doi:10.1093/toxsci/kfr061.
57. Miller, W.L.; Tee, M.K. The Post-Translational Regulation of 17,20 Lyase Activity. Mol. Cell. Endocrinol. 2015, 408, 99–106, doi:10.1016/j.mce.2014.09.010.
58. Peters, A.E.; Ford, E.A.; Roman, S.D.; Bromfield, E.G.; Nixon, B.; Pringle, K.G.; Sutherland, J.M. Impact of Bisphenol A and Its Alternatives on Oocyte Health: A Scoping Review. Hum. Reprod. Update 2024, 30, 653–691, doi:10.1093/humupd/dmae025.
59. Zahra, Z.; Khan, M.R.; Majid, M.; Maryam, S.; Sajid, M. Gonadoprotective Ability of Vincetoxicum Arnottianum Extract against Bisphenol A-Induced Testicular Toxicity and Hormonal Imbalance in Male Sprague Dawley Rats. Andrologia 2020, 52, e13590, doi:10.1111/and.13590.
60. Galloway, T.; Cipelli, R.; Guralnik, J.; Ferrucci, L.; Bandinelli, S.; Corsi, A.M.; Money, C.; McCormack, P.; Melzer, D. Daily Bisphenol A Excretion and Associations with Sex Hormone Concentrations: Results from the InCHIANTI Adult Population Study. Environ. Health Perspect. 2010, 118, 1603–1608, doi:10.1289/ehp.1002367.
61. Basu, B.R.; Chowdhury, O.; Saha, S.K. Possible Link between Stress-Related Factors and Altered Body Composition in Women with Polycystic Ovarian Syndrome. J. Hum. Reprod. Sci. 2018, 11, 10–18, doi:10.4103/jhrs.JHRS_78_17.
62. Papalou, O.; Diamanti-Kandarakis, E. The Role of Stress in PCOS. Expert Rev. Endocrinol. Metab. 2017, 12, 87–95, doi:10.1080/17446651.2017.1266250.
63. Francisco, V.; Pino, J.; Gonzalez-Gay, M.A.; Mera, A.; Lago, F.; Gómez, R.; Mobasheri, A.; Gualillo, O. Adipokines and Inflammation: Is It a Question of Weight?: Obesity and Inflammatory Diseases. Br. J. Pharmacol. 2018, 175, 1569–1579, doi:10.1111/bph.14181.
64. Vojnović Milutinović, D.; Teofilović, A.; Veličković, N.; Brkljačić, J.; Jelača, S.; Djordjevic, A.; Macut, D. Glucocorticoid Signaling and Lipid Metabolism Disturbances in the Liver of Rats Treated with 5α-Dihydrotestosterone in an Animal Model of Polycystic Ovary Syndrome. Endocrine 2021, 72, 562–572, doi:10.1007/s12020-020-02600-1.
65. Benjamin, J.J.; Kuppusamy, M.; Koshy, T.; Kalburgi Narayana, M.; Ramaswamy, P. Cortisol and Polycystic Ovarian Syndrome - a Systematic Search and Meta-Analysis of Case-Control Studies. Gynecol. Endocrinol. 2021, 37, 961–967, doi:10.1080/09513590.2021.1908254.
66. Wiweko, B.; Indra, I.; Susanto, C.; Natadisastra, M.; Hestiantoro, A. The Correlation between Serum AMH and HOMA-IR among PCOS Phenotypes. BMC Res. Notes 2018, 11, 114, doi:10.1186/s13104-018-3207-y.
67. Md Muslim, M.Z.; Mohammed Jelani, A.; Shafii, N.; Yaacob, N.M.; Che Soh, N.A.A.; Ibrahim, H.A. Correlation between Anti-Mullerian Hormone with Insulin Resistance in Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis. J. Ovarian Res. 2024, 17, 106, doi:10.1186/s13048-024-01436-x.
68. Pratama, G.; Wiweko, B.; Asmarinah; Widyahening, I.S.; Andraini, T.; Bayuaji, H.; Hestiantoro, A. Mechanism of Elevated LH/FSH Ratio in Lean PCOS Revisited: A Path Analysis. Sci. Rep. 2024, 14, 8229, doi:10.1038/s41598-024-58064-0.
69. Singh, S.; Kaur, M.; Beri, A.; Kaur, A. Significance of LHCGR Polymorphisms in Polycystic Ovary Syndrome: An Association Study. Sci. Rep. 2023, 13, 22841, doi:10.1038/s41598-023-48881-0.
70. Hattori, N.; Fujiwara, H.; Maeda, M.; Fujii, S.; Ueda, M. Epoxide Hydrolase Affects Estrogen Production in the Human Ovary. Endocrinology 2000, 141, 3353–3365, doi:10.1210/endo.141.9.7682.
71. Sang, Q.; Li, X.; Wang, H.; Wang, H.; Zhang, S.; Feng, R.; Xu, Y.; Li, Q.; Zhao, X.; Xing, Q.; et al. Quantitative Methylation Level of the EPHX1 Promoter in Peripheral Blood DNA Is Associated with Polycystic Ovary Syndrome. PLoS One 2014, 9, e88013, doi:10.1371/journal.pone.0088013.

72. Bogacka, I.; Kurzynska, A.; Bogacki, M.; Chojnowska, K. Peroxisome Proliferator-Activated Receptors in the Regulation of Female Reproductive Functions. Folia Histochem. Cytobiol. 2015, 53, 189–200, doi:10.5603/fhc.a2015.0023.
73. Vitti, M.; Di Emidio, G.; Di Carlo, M.; Carta, G.; Antonosante, A.; Artini, P.G.; Cimini, A.; Tatone, C.; Benedetti, E. Peroxisome Proliferator-Activated Receptors in Female Reproduction and Fertility. PPAR Res. 2016, 2016, 4612306, doi:10.1155/2016/4612306.
74. Psilopatis, I.; Vrettou, K.; Nousiopoulou, E.; Palamaris, K.; Theocharis, S. The Role of Peroxisome Proliferator-Activated Receptors in Polycystic Ovary Syndrome. J. Clin. Med. 2023, 12, doi:10.3390/jcm12082912.
75. Zhao, H.; Zhang, J.; Cheng, X.; Nie, X.; He, B. Insulin Resistance in Polycystic Ovary Syndrome across Various Tissues: An Updated Review of Pathogenesis, Evaluation, and Treatment. J. Ovarian Res. 2023, 16, 9, doi:10.1186/s13048-022-01091-0.
76. Hayes, E.; Winston, N.; Stocco, C. Molecular Crosstalk between Insulin-like Growth Factors and Follicle-Stimulating Hormone in the Regulation of Granulosa Cell Function. Reprod. Med. Biol. 2024, 23, e12575, doi:10.1002/rmb2.12575.
77. Piau, T.B.; de Queiroz Rodrigues, A.; Paulini, F. Insulin-like Growth Factor (IGF) Performance in Ovarian Function and Applications in Reproductive Biotechnologies. Growth Horm. IGF Res. 2023, 72–73, 101561, doi:10.1016/j.ghir.2023.101561.
78. Carpentier, A.C. 100th Anniversary of the Discovery of Insulin Perspective: Insulin and Adipose Tissue Fatty Acid Metabolism. Am. J. Physiol. Endocrinol. Metab. 2021, 320, E653–E670, doi:10.1152/ajpendo.00620.2020.
79. Escobar-Morreale, H.F.; Luque-Ramírez, M.; González, F. Circulating Inflammatory Markers in Polycystic Ovary Syndrome: A Systematic Review and Metaanalysis. Fertil. Steril. 2011, 95, 1048-58.e1-2, doi:10.1016/j.fertnstert.2010.11.036.
80. Aboeldalyl, S.; James, C.; Seyam, E.; Ibrahim, E.M.; Shawki, H.E.-D.; Amer, S. The Role of Chronic Inflammation in Polycystic Ovarian Syndrome-A Systematic Review and Meta-Analysis. Int. J. Mol. Sci. 2021, 22, 2734, doi:10.3390/ijms22052734.
81. Liu, Y.; Shao, Y.; Xie, J.; Chen, L.; Zhu, G. The Efficacy and Safety of Metformin Combined with Simvastatin in the Treatment of Polycystic Ovary Syndrome: A Meta-Analysis and Systematic Review: A Meta-Analysis and Systematic Review. Medicine (Baltimore) 2021, 100, e26622, doi:10.1097/MD.0000000000026622.
82. Shabbir, S.; Khurram, E.; Moorthi, V.S.; Eissa, Y.T.H.; Kamal, M.A.; Butler, A.E. The Interplay between Androgens and the Immune Response in Polycystic Ovary Syndrome. J. Transl. Med. 2023, 21, 259, doi:10.1186/s12967-023-04116-4.
83. Abraham Gnanadass, S.; Divakar Prabhu, Y.; Valsala Gopalakrishnan, A. Association of Metabolic and Inflammatory Markers with Polycystic Ovarian Syndrome (PCOS): An Update. Arch. Gynecol. Obstet. 2021, 303, 631–643, doi:10.1007/s00404-020-05951-2.
84. Field, S.L.; Dasgupta, T.; Cummings, M.; Orsi, N.M. Cytokines in Ovarian Folliculogenesis, Oocyte Maturation and Luteinisation: Cytokines in Folliculogenesis. Mol. Reprod. Dev. 2014, 81, 284–314, doi:10.1002/mrd.22285.
85. Zhai, Y.; Pang, Y. Systemic and Ovarian Inflammation in Women with Polycystic Ovary Syndrome. J. Reprod. Immunol. 2022, 151, 103628, doi:10.1016/j.jri.2022.103628.
86. Navarro-Pando, J.M.; Alcocer-Gómez, E.; Castejón-Vega, B.; Navarro-Villarán, E.; Condés-Hervás, M.; Mundi-Roldan, M.; Muntané, J.; Pérez-Pulido, A.J.; Bullon, P.; Wang, C.; et al. Inhibition of the NLRP3 Inflammasome Prevents Ovarian Aging. Sci. Adv. 2021, 7, eabc7409, doi:10.1126/sciadv.abc7409.
87. Wu, H.; Yu, K.; Yang, Z. Associations between TNF-α and Interleukin Gene Polymorphisms with Polycystic Ovary Syndrome Risk: A Systematic Review and Meta-Analysis. J. Assist. Reprod. Genet. 2015, 32, 625–634, doi:10.1007/s10815-015-0449-7.
88. Alkhuriji, A.F.; Al Omar, S.Y.; Babay, Z.A.; El-Khadragy, M.F.; Mansour, L.A.; Alharbi, W.G.; Khalil, M.I. Association of IL-1β, IL-6, TNF-α, and TGFβ1 Gene Polymorphisms with Recurrent Spontaneous Abortion in Polycystic Ovary Syndrome. Dis. Markers 2020, 2020, 6076274, doi:10.1155/2020/6076274.

89. Yuan, K.; Zhang, Y. Oxidative Stress and Antioxidant Strategies in Human Diseases. In Oxidative Stress; Springer Singapore: Singapore, 2021; pp. 1–26 ISBN 9789811605215.
90. Zarkovic, N. Roles and Functions of ROS and RNS in Cellular Physiology and Pathology. Cells 2020, 9, 767, doi:10.3390/cells9030767.
91. Di Meo, S.; Reed, T.T.; Venditti, P.; Victor, V.M. Role of ROS and RNS Sources in Physiological and Pathological Conditions. Oxid. Med. Cell. Longev. 2016, 2016, 1245049, doi:10.1155/2016/1245049.
92. Yan, F.; Zhao, Q.; Li, Y.; Zheng, Z.; Kong, X.; Shu, C.; Liu, Y.; Shi, Y. The Role of Oxidative Stress in Ovarian Aging: A Review. J. Ovarian Res. 2022, 15, 100, doi:10.1186/s13048-022-01032-x.
93. Lalonde-Bester, S.; Malik, M.; Masoumi, R.; Ng, K.; Sidhu, S.; Ghosh, M.; Vine, D. Prevalence and Etiology of Eating Disorders in Polycystic Ovary Syndrome: A Scoping Review. Adv. Nutr. 2024, 15, 100193, doi:10.1016/j.advnut.2024.100193.
94. Juan, C.A.; Pérez de la Lastra, J.M.; Plou, F.J.; Pérez-Lebeña, E. The Chemistry of Reactive Oxygen Species (ROS) Revisited: Outlining Their Role in Biological Macromolecules (DNA, Lipids and Proteins) and Induced Pathologies. Int. J. Mol. Sci. 2021, 22, 4642, doi:10.3390/ijms22094642.
95. Morgan, M.J.; Liu, Z.-G. Crosstalk of Reactive Oxygen Species and NF-κB Signaling. Cell Res. 2011, 21, 103–115, doi:10.1038/cr.2010.178.
96. Lingappan, K. NF-κB in Oxidative Stress. Curr. Opin. Toxicol. 2018, 7, 81–86, doi:10.1016/j.cotox.2017.11.002.
97. Murri, M.; Luque-Ramírez, M.; Insenser, M.; Ojeda-Ojeda, M.; Escobar-Morreale, H.F. Circulating Markers of Oxidative Stress and Polycystic Ovary Syndrome (PCOS): A Systematic Review and Meta-Analysis. Hum. Reprod. Update 2013, 19, 268–288, doi:10.1093/humupd/dms059.
98. Guerreiro, V.A.; Carvalho, D.; Freitas, P. Obesity, Adipose Tissue, and Inflammation Answered in Questions. J. Obes. 2022, 2022, 2252516, doi:10.1155/2022/2252516.
99. Savulescu-Fiedler, I.; Mihalcea, R.; Dragosloveanu, S.; Scheau, C.; Baz, R.O.; Caruntu, A.; Scheau, A.-E.; Caruntu, C.; Benea, S.N. The Interplay between Obesity and Inflammation. Life (Basel) 2024, 14, 856, doi:10.3390/life14070856.
100. Hildebrandt, X.; Ibrahim, M.; Peltzer, N. Cell Death and Inflammation during Obesity: "Know My Methods, WAT(Son)." Cell Death Differ. 2023, 30, 279–292, doi:10.1038/s41418-022-01062-4.
101. Han, S.M.; Nahmgoong, H.; Yim, K.M.; Kim, J.B. How Obesity Affects Adipocyte Turnover. Trends Endocrinol. Metab. 2024, doi:10.1016/j.tem.2024.07.004.
102. Karpe, F.; Dickmann, J.R.; Frayn, K.N. Fatty Acids, Obesity, and Insulin Resistance: Time for a Reevaluation. Diabetes 2011, 60, 2441–2449, doi:10.2337/db11-0425.
103. Bril, F.; Ezeh, U.; Amiri, M.; Hatoum, S.; Pace, L.; Chen, Y.-H.; Bertrand, F.; Gower, B.; Azziz, R. Adipose Tissue Dysfunction in Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 2023, 109, 10–24, doi:10.1210/clinem/dgad356.
104. Jocken, J.W.E.; Blaak, E.E. Catecholamine-Induced Lipolysis in Adipose Tissue and Skeletal Muscle in Obesity. Physiol. Behav. 2008, 94, 219–230, doi:10.1016/j.physbeh.2008.01.002.
105. Arner, P. Catecholamine-Induced Lipolysis in Obesity. Int. J. Obes. Relat. Metab. Disord. 1999, 23 Suppl 1, 10–13, doi:10.1038/sj.ijo.0800789.
106. Kang, Z.F.; Deng, Y.; Zhou, Y.; Fan, R.R.; Chan, J.C.N.; Laybutt, D.R.; Luzuriaga, J.; Xu, G. Pharmacological Reduction of NEFA Restores the Efficacy of Incretin-Based Therapies through GLP-1 Receptor Signalling in the Beta Cell in Mouse Models of Diabetes. Diabetologia 2013, 56, 423–433, doi:10.1007/s00125-012-2776-x.
107. Chueire, V.B.; Muscelli, E. Effect of Free Fatty Acids on Insulin Secretion, Insulin Sensitivity and Incretin Effect - a Narrative Review. Arch. Endocrinol. Metab. 2021, 65, 24–31, doi:10.20945/2359-3997000000313.
108. Lizneva, D.; Suturina, L.; Walker, W.; Brakta, S.; Gavrilova-Jordan, L.; Azziz, R. Criteria, Prevalence, and Phenotypes of Polycystic Ovary Syndrome. Fertil. Steril. 2016, 106, 6–15, doi:10.1016/j.fertnstert.2016.05.003.
109. Khan, M.J.; Ullah, A.; Basit, S. Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. Appl. Clin. Genet. 2019, 12, 249–260, doi:10.2147/TACG.S200341.

110. Siddiqui, S.; Mateen, S.; Ahmad, R.; Moin, S. A Brief Insight into the Etiology, Genetics, and Immunology of Polycystic Ovarian Syndrome (PCOS). J. Assist. Reprod. Genet. 2022, 39, 2439–2473, doi:10.1007/s10815-022-02625-7.
111. Domecq, J.P.; Prutsky, G.; Mullan, R.J.; Hazem, A.; Sundaresh, V.; Elamin, M.B.; Phung, O.J.; Wang, A.; Hoeger, K.; Pasquali, R.; et al. Lifestyle Modification Programs in Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. J. Clin. Endocrinol. Metab. 2013, 98, 4655–4663, doi:10.1210/jc.2013-2385.
112. Moran, L.J.; Hutchison, S.K.; Norman, R.J.; Teede, H.J. Lifestyle Changes in Women with Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2011, CD007506, doi:10.1002/14651858.CD007506.pub3.
113. Shang, Y.; Zhou, H.; Hu, M.; Feng, H. Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 2020, 105, 3346–3360, doi:10.1210/clinem/dgaa425.
114. González, F.; Considine, R.V.; Abdelhadi, O.A.; Acton, A.J. Inflammation Triggered by Saturated Fat Ingestion Is Linked to Insulin Resistance and Hyperandrogenism in Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 2020, 105, e2152–e2167, doi:10.1210/clinem/dgaa108.
115. González, F.; Considine, R.V.; Abdelhadi, O.A.; Xue, J.; Acton, A.J. Saturated Fat Ingestion Stimulates Proatherogenic Inflammation in Polycystic Ovary Syndrome. Am. J. Physiol. Endocrinol. Metab. 2021, 321, E689–E701, doi:10.1152/ajpendo.00213.2021.
116. Hung, H.-C.; Tsai, S.-F.; Chou, H.-W.; Tsai, M.-J.; Hsu, P.-L.; Kuo, Y.-M. Dietary Fatty Acids Differentially Affect Secretion of Pro-Inflammatory Cytokines in Human THP-1 Monocytes. Sci. Rep. 2023, 13, 5511, doi:10.1038/s41598-023-32710-5.
117. Fang, F.; Ni, K.; Cai, Y.; Shang, J.; Zhang, X.; Xiong, C. Effect of Vitamin D Supplementation on Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Complement. Ther. Clin. Pract. 2017, 26, 53–60, doi:10.1016/j.ctcp.2016.11.008.
118. Mohan, A.; Haider, R.; Fakhor, H.; Hina, F.; Kumar, V.; Jawed, A.; Majumder, K.; Ayaz, A.; Lal, P.M.; Tejwaney, U.; et al. Vitamin D and Polycystic Ovary Syndrome (PCOS): A Review. Ann. Med. Surg. (Lond.) 2023, 85, 3506–3511, doi:10.1097/MS9.0000000000000879.
119. Han, Y.; Cao, Q.; Qiao, X.; Huang, W. Effect of Vitamin D Supplementation on Hormones and Menstrual Cycle Regularization in Polycystic Ovary Syndrome Women: A Systemic Review and Meta-Analysis. J. Obstet. Gynaecol. Res. 2023, 49, 2232–2244, doi:10.1111/jog.15727.
120. ACOG committee. Screening and Management of the Hyperandrogenic Adolescent: ACOG Committee Opinion, Number 789. Obstet. Gynecol. 2019, 134, e106–e114, doi:10.1097/aog.0000000000003475.
121. Azziz, R.; Carmina, E.; Dewailly, D.; Diamanti-Kandarakis, E.; Escobar-Morreale, H.F.; Futterweit, W.; Janssen, O.E.; Legro, R.S.; Norman, R.J.; Taylor, A.E.; et al. The Androgen Excess and PCOS Society Criteria for the Polycystic Ovary Syndrome: The Complete Task Force Report. Fertil. Steril. 2009, 91, 456–488, doi:10.1016/j.fertnstert.2008.06.035.
122. Ollila, M.M.; West, S.; Keinänen-Kiukaanniemi, S.; Jokelainen, J.; Auvinen, J.; Puukka, K.; Ruokonen, A.; Järvelin, M.-R.; Tapanainen, J.S.; Franks, S.; et al. Overweight and Obese but Not Normal Weight Women with PCOS Are at Increased Risk of Type 2 Diabetes Mellitus-a Prospective, Population-Based Cohort Study. Hum. Reprod. 2017, 32, 423–431, doi:10.1093/humrep/dew329.
123. Ryu, K.-J.; Kim, M.S.; Kim, H.K.; Kim, Y.J.; Yi, K.W.; Shin, J.H.; Hur, J.Y.; Kim, T.; Park, H. Risk of Type 2 Diabetes Is Increased in Nonobese Women with Polycystic Ovary Syndrome: The National Health Insurance Service-National Sample Cohort Study. Fertil. Steril. 2021, 115, 1569–1575, doi:10.1016/j.fertnstert.2020.12.018.
124. Brutocao, C.; Zaiem, F.; Alsawas, M.; Morrow, A.S.; Murad, M.H.; Javed, A. Psychiatric Disorders in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Endocrine 2018, 62, 318–325, doi:10.1007/s12020-018-1692-3.
125. Douglas, K.M.; Fenton, A.J.; Eggleston, K.; Porter, R.J. Rate of Polycystic Ovary Syndrome in Mental Health Disorders: A Systematic Review. Arch. Womens. Ment. Health 2022, 25, 9–19, doi:10.1007/s00737-021-01179-4.
126. Tabassum, F.; Jyoti, C.; Sinha, H.H.; Dhar, K.; Akhtar, M.S. Impact of Polycystic Ovary Syndrome on Quality of Life of Women in Correlation to Age, Basal Metabolic Index, Education and Marriage. PLoS One 2021, 16, e0247486, doi:10.1371/journal.pone.0247486.

127. Wan, Z.; Zhao, J.; Ye, Y.; Sun, Z.; Li, K.; Chen, Y.; Fang, Y.; Zhang, Y.; Lin, J.; Sun, P.; et al. Risk and Incidence of Cardiovascular Disease Associated with Polycystic Ovary Syndrome. Eur. J. Prev. Cardiol. 2024, 31, 1560–1570, doi:10.1093/eurjpc/zwae066.
128. Osibogun, O.; Ogunmoroti, O.; Michos, E.D. Polycystic Ovary Syndrome and Cardiometabolic Risk: Opportunities for Cardiovascular Disease Prevention. Trends Cardiovasc. Med. 2020, 30, 399–404, doi:10.1016/j.tcm.2019.08.010.
129. Wekker, V.; van Dammen, L.; Koning, A.; Heida, K.Y.; Painter, R.C.; Limpens, J.; Laven, J.S.E.; Roeters van Lennep, J.E.; Roseboom, T.J.; Hoek, A. Long-Term Cardiometabolic Disease Risk in Women with PCOS: A Systematic Review and Meta-Analysis. Hum. Reprod. Update 2020, 26, 942–960, doi:10.1093/humupd/dmaa029.
130. Meyer, M.L.; Malek, A.M.; Wild, R.A.; Korytkowski, M.T.; Talbott, E.O. Carotid Artery Intima-Media Thickness in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Hum. Reprod. Update 2012, 18, 112–126, doi:10.1093/humupd/dmr046.
131. Osibogun, O.; Ogunmoroti, O.; Kolade, O.B.; Hays, A.G.; Okunrintemi, V.; Minhas, A.S.; Gulati, M.; Michos, E.D. A Systematic Review and Meta-Analysis of the Association between Polycystic Ovary Syndrome and Coronary Artery Calcification. J. Womens. Health (Larchmt) 2022, 31, 762–771, doi:10.1089/jwh.2021.0608.
132. Lo, J.C.; Feigenbaum, S.L.; Yang, J.; Pressman, A.R.; Selby, J.V.; Go, A.S. Epidemiology and Adverse Cardiovascular Risk Profile of Diagnosed Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 2006, 91, 1357–1363, doi:10.1210/jc.2005-2430.
133. Yu, H.-F.; Chen, H.-S.; Rao, D.-P.; Gong, J. Association between Polycystic Ovary Syndrome and the Risk of Pregnancy Complications: A PRISMA-Compliant Systematic Review and Meta-Analysis. Medicine (Baltimore) 2016, 95, e4863, doi:10.1097/MD.0000000000004863.
134. Pan, H.; Xian, P.; Yang, D.; Zhang, C.; Tang, H.; He, X.; Lin, H.; Wen, X.; Ma, H.; Lai, M. Polycystic Ovary Syndrome Is an Independent Risk Factor for Hypertensive Disorders of Pregnancy: A Systematic Review, Meta-Analysis, and Meta-Regression. Endocrine 2021, 74, 518–529, doi:10.1007/s12020-021-02886-9.
135. The Centers for Disease Control and Prevention QuickStats: Percentage of Mothers with Gestational Diabetes,* by Maternal Age - National Vital Statistics System, United States, 2016 and 2021. MMWR Morb. Mortal. Wkly. Rep. 2023, 72, 16, doi:10.15585/mmwr.mm7201a4.
136. Sweeting, A.; Hannah, W.; Backman, H.; Catalano, P.; Feghali, M.; Herman, W.H.; Hivert, M.-F.; Immanuel, J.; Meek, C.; Oppermann, M.L.; et al. Epidemiology and Management of Gestational Diabetes. Lancet 2024, 404, 175–192, doi:10.1016/S0140-6736(24)00825-0.
137. Plows, J.F.; Stanley, J.L.; Baker, P.N.; Reynolds, C.M.; Vickers, M.H. The Pathophysiology of Gestational Diabetes Mellitus. Int. J. Mol. Sci. 2018, 19, 3342, doi:10.3390/ijms19113342.
138. Legro, R.S.; Zaino, R.J.; Demers, L.M.; Kunselman, A.R.; Gnatuk, C.L.; Williams, N.I.; Dodson, W.C. The Effects of Metformin and Rosiglitazone, Alone and in Combination, on the Ovary and Endometrium in Polycystic Ovary Syndrome. Am. J. Obstet. Gynecol. 2007, 196, 402.e1-10; discussion 402.e10-1, doi:10.1016/j.ajog.2006.12.025.
139. Choudhury, A.A.; Rajeswari, V.D. Polycystic Ovary Syndrome (PCOS) Increases the Risk of Subsequent Gestational Diabetes Mellitus (GDM): A Novel Therapeutic Perspective. Life Sci. 2022, 310, 121069, doi:10.1016/j.lfs.2022.121069.
140. Holte, J.; Gennarelli, G.; Wide, L.; Lithell, H.; Berne, C. High Prevalence of Polycystic Ovaries and Associated Clinical, Endocrine, and Metabolic Features in Women with Previous Gestational Diabetes Mellitus. J. Clin. Endocrinol. Metab. 1998, 83, 1143–1150, doi:10.1210/jcem.83.4.4707.
141. Koivunen, R.M.; Juutinen, J.; Vauhkonen, I.; Morin-Papunen, L.C.; Ruokonen, A.; Tapanainen, J.S. Metabolic and Steroidogenic Alterations Related to Increased Frequency of Polycystic Ovaries in Women with a History of Gestational Diabetes. J. Clin. Endocrinol. Metab. 2001, 86, 2591–2599, doi:10.1210/jcem.86.6.7612.
142. Qiu, Y.; Zhang, X.; Ni, Y. Association between Polycystic Ovarian Syndrome and Risk of Gestational Diabetes Mellitus: A Meta-Analysis. Gynecol. Obstet. Invest. 2022, 87, 150–158, doi:10.1159/000521728.

143. Guo, X.; Yao, Y.; Wang, T.; Wu, J.; Jiang, R. The Impact of Hyperandrogenemia on Pregnancy Complications and Outcomes in Patients with PCOS: A Systematic Review and Meta-Analysis. Hypertens. Pregnancy 2024, 43, 2379389, doi:10.1080/10641955.2024.2379389.
144. Herman, R.; Sikonja, J.; Jensterle, M.; Janez, A.; Dolzan, V. Insulin Metabolism in Polycystic Ovary Syndrome: Secretion, Signaling, and Clearance. Int. J. Mol. Sci. 2023, 24, doi:10.3390/ijms24043140.
145. National Cancer Institute Obesity and Cancer Available online: https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet (accessed on 25 December 2024).
146. Onstad, M.A.; Schmandt, R.E.; Lu, K.H. Addressing the Role of Obesity in Endometrial Cancer Risk, Prevention, and Treatment. J. Clin. Oncol. 2016, 34, 4225–4230, doi:10.1200/jco.2016.69.4638.
147. Ling, S.; Brown, K.; Miksza, J.K.; Howells, L.M.; Morrison, A.; Issa, E.; Yates, T.; Khunti, K.; Davies, M.J.; Zaccardi, F. Risk of Cancer Incidence and Mortality Associated with Diabetes: A Systematic Review with Trend Analysis of 203 Cohorts. Nutr. Metab. Cardiovasc. Dis. 2021, 31, 14–22, doi:10.1016/j.numecd.2020.09.023
148. Hernandez, A.V.; Pasupuleti, V.; Benites-Zapata, V.A.; Thota, P.; Deshpande, A.; Perez-Lopez, F.R. Insulin Resistance and Endometrial Cancer Risk: A Systematic Review and Meta-Analysis. Eur. J. Cancer 2015, 51, 2747–2758, doi:10.1016/j.ejca.2015.08.031.
149. Ding, D.-C.; Chen, W.; Wang, J.-H.; Lin, S.-Z. Association between Polycystic Ovarian Syndrome and Endometrial, Ovarian, and Breast Cancer: A Population-Based Cohort Study in Taiwan. Medicine (Baltimore) 2018, 97, e12608, doi:10.1097/md.0000000000012608.
150. Meczekalski, B.; Pérez-Roncero, G.R.; López-Baena, M.T.; Chedraui, P.; Pérez-López, F.R. The Polycystic Ovary Syndrome and Gynecological Cancer Risk. Gynecol. Endocrinol. 2020, 36, 289–293, doi:10.1080/09513590.2020.1730794.
151. Renehan, A.G.; Tyson, M.; Egger, M.; Heller, R.F.; Zwahlen, M. Body-Mass Index and Incidence of Cancer: A Systematic Review and Meta-Analysis of Prospective Observational Studies. Lancet 2008, 371, 569–578, doi:10.1016/s0140-6736(08)60269-x.
152. Ho, S.-M. Estrogen, Progesterone and Epithelial Ovarian Cancer. Reprod. Biol. Endocrinol. 2003, 1, doi:10.1186/1477-7827-1-73.
153. Harris, H.R.; Titus, L.J.; Cramer, D.W.; Terry, K.L. Long and Irregular Menstrual Cycles, Polycystic Ovary Syndrome, and Ovarian Cancer Risk in a Population-based Case-control Study. Int. J. Cancer 2017, 140, 285–291, doi:10.1002/ijc.30441.
154. National institute of child health. How Do Health Care Providers Diagnose PCOS? Available online: https://www.nichd.nih.gov/health/topics/pcos/conditioninfo/diagnose (accessed on 25 December 2024).
155. National Institute of Health Evidence-Based Methodology Workshop on Polycystic Ovary Syndrome (PCOS) Available online: https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/evidence-based-methodology-workshop-polycystic-ovary-syndrome-pcos (accessed on 25 December 2024).
156. Teede, H.J.; Tay, C.T.; Laven, J.J.E.; Dokras, A.; Moran, L.J.; Piltonen, T.T.; Costello, M.F.; Boivin, J.; Redman, L.M.; Boyle, J.A.; et al. Recommendations from the 2023 International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 2023, 108, 2447–2469, doi:10.1210/clinem/dgad463.
157. Dewailly, D.; Lujan, M.E.; Carmina, E.; Cedars, M.I.; Laven, J.; Norman, R.J.; Escobar-Morreale, H.F. Definition and Significance of Polycystic Ovarian Morphology: A Task Force Report from the Androgen Excess and Polycystic Ovary Syndrome Society. Hum. Reprod. Update 2014, 20, 334–352, doi:10.1093/humupd/dmt061.
158. Nsugbe, E. An Artificial Intelligence-Based Decision Support System for Early Diagnosis of Polycystic Ovaries Syndrome. Healthcare Analytics 2023, 3, 100164, doi:10.1016/j.health.2023.100164.
159. Lim, S.S.; Hutchison, S.K.; Van Ryswyk, E.; Norman, R.J.; Teede, H.J.; Moran, L.J. Lifestyle Changes in Women with Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2019, 3, CD007506, doi:10.1002/14651858.CD007506.pub4.
160. Best, D.; Bhattacharya, S. Obesity and Fertility. Horm. Mol. Biol. Clin. Investig. 2015, 24, 5–10, doi:10.1515/hmbci-2015-0023.

 doi:10.20944/preprints202412.2399.v1

161. Wang, A.; Mo, T.; Li, Q.; Shen, C.; Liu, M. The Effectiveness of Metformin, Oral Contraceptives, and Lifestyle Modification in Improving the Metabolism of Overweight Women with Polycystic Ovary Syndrome: A Network Meta-Analysis. Endocrine 2019, 64, 220–232, doi:10.1007/s12020-019-01860-w.
162. Phelan, N.; O'Connor, A.; Kyaw Tun, T.; Correia, N.; Boran, G.; Roche, H.M.; Gibney, J. Hormonal and Metabolic Effects of Polyunsaturated Fatty Acids in Young Women with Polycystic Ovary Syndrome: Results from a Cross-Sectional Analysis and a Randomized, Placebo-Controlled, Crossover Trial. Am. J. Clin. Nutr. 2011, 93, 652–662, doi:10.3945/ajcn.110.005538.
163. Rahmani, E.; Samimi, M.; Ebrahimi, F.A.; Foroozanfard, F.; Ahmadi, S.; Rahimi, M.; Jamilian, M.; Aghadavod, E.; Bahmani, F.; Taghizadeh, M.; et al. The Effects of Omega-3 Fatty Acids and Vitamin E Co-Supplementation on Gene Expression of Lipoprotein(a) and Oxidized Low-Density Lipoprotein, Lipid Profiles and Biomarkers of Oxidative Stress in Patients with Polycystic Ovary Syndrome. Mol. Cell. Endocrinol. 2017, 439, 247–255, doi:10.1016/j.mce.2016.09.008.
164. Hajishafiee, M.; Askari, G.; Iranj, B.; Ghiasvand, R.; Bellissimo, N.; Totosy de Zepetnek, J.; Salehi-Abargouei, A. The Effect of N-3 Polyunsaturated Fatty Acid Supplementation on Androgen Status in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Clinical Trials. Horm. Metab. Res. 2016, 48, 281–289, doi:10.1055/s-0042-105288.
165. Mitra, S.; Nayak, P.K.; Agrawal, S. Laparoscopic Ovarian Drilling: An Alternative but Not the Ultimate in the Management of Polycystic Ovary Syndrome. J. Nat. Sci. Biol. Med. 2015, 6, 40–48, doi:10.4103/0976-9668.149076.
166. Gadalla, M.A.; Norman, R.J.; Tay, C.T.; Hiam, D.S.; Melder, A.; Pundir, J.; Thangaratinam, S.; Teede, H.J.; Mol, B.W.J.; Moran, L.J. Medical and Surgical Treatment of Reproductive Outcomes in Polycystic Ovary Syndrome: An Overview of Systematic Reviews. Int. J. Fertil. Steril. 2020, 13, 257–270, doi:10.22074/ijfs.2020.5608.
167. Forslund, M.; Melin, J.; Alesi, S.; Piltonen, T.; Romualdi, D.; Tay, C.T.; Witchel, S.; Pena, A.; Mousa, A.; Teede, H. Different Kinds of Oral Contraceptive Pills in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Eur. J. Endocrinol. 2023, 189, S1–S16, doi:10.1093/ejendo/lvad082.
168. Alesi, S.; Forslund, M.; Melin, J.; Romualdi, D.; Peña, A.; Tay, C.T.; Witchel, S.F.; Teede, H.; Mousa, A. Efficacy and Safety of Anti-Androgens in the Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. EClinicalMedicine 2023, 63, 102162, doi:10.1016/j.eclinm.2023.102162.
169. Elenis, E.; Desroziers, E.; Persson, S.; Sundström Poromaa, I.; Campbell, R.E. Early Initiation of Anti-Androgen Treatment Is Associated with Increased Probability of Spontaneous Conception Leading to Childbirth in Women with Polycystic Ovary Syndrome: A Population-Based Multiregistry Cohort Study in Sweden. Hum. Reprod. 2021, 36, 1427–1435, doi:10.1093/humrep/deaa357.
170. Barrionuevo, P.; Nabhan, M.; Altayar, O.; Wang, Z.; Erwin, P.J.; Asi, N.; Martin, K.A.; Murad, M.H. Treatment Options for Hirsutism: A Systematic Review and Network Meta-Analysis. J. Clin. Endocrinol. Metab. 2018, 103, 1258–1264, doi:10.1210/jc.2017-02052.
171. Wolf, J.E., Jr; Shander, D.; Huber, F.; Jackson, J.; Lin, C.-S.; Mathes, B.M.; Schrode, K.; the Eflornithine HCl Study Group Randomized, Double-blind Clinical Evaluation of the Efficacy and Safety of Topical Eflornithine HCl 13.9% Cream in the Treatment of Women with Facial Hair. Int. J. Dermatol. 2007, 46, 94–98, doi:10.1111/j.1365-4632.2006.03079.x.
172. Jackson, J.; Caro, J.J.; Caro, G.; Garfield, F.; Huber, F.; Zhou, W.; Lin, C.-S.; Shander, D.; Schrode, K.; Eflornithine HCl Study Group The Effect of Eflornithine 13.9% Cream on the Bother and Discomfort Due to Hirsutism. Int. J. Dermatol. 2007, 46, 976–981, doi:10.1111/j.1365-4632.2007.03270.x.
173. Smith, S.R.; Piacquadio, D.J.; Beger, B.; Littler, C. Eflornithine Cream Combined with Laser Therapy in the Management of Unwanted Facial Hair Growth in Women: A Randomized Trial. Dermatol. Surg. 2006, 32, 1237–1243, doi:10.1111/j.1524-4725.2006.32282.x.
174. Melin, J.; Forslund, M.; Alesi, S.; Piltonen, T.; Romualdi, D.; Spritzer, P.M.; Tay, C.T.; Pena, A.; Witchel, S.F.; Mousa, A.; et al. The Impact of Metformin with or without Lifestyle Modification versus Placebo on Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Eur. J. Endocrinol. 2023, 189, S37–S63, doi:10.1093/ejendo/lvad098.

175. Melin, J.; Forslund, M.; Alesi, S.; Piltonen, T.; Romualdi, D.; Spritzer, P.M.; Tay, C.T.; Pena, A.; Witchel, S.F.; Mousa, A.; et al. Metformin and Combined Oral Contraceptive Pills in the Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. J. Clin. Endocrinol. Metab. 2024, 109, e817–e836, doi:10.1210/clinem/dgad465.
176. Melin, J.M.; Forslund, M.; Alesi, S.J.; Piltonen, T.; Romualdi, D.; Spritzer, P.M.; Tay, C.T.; Pena, A.S.; Witchel, S.F.; Mousa, A.; et al. Effects of Different Insulin Sensitisers in the Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Clin. Endocrinol. (Oxf.) 2024, 100, 149–163, doi:10.1111/cen.14983.
177. Abdalla, M.A.; Shah, N.; Deshmukh, H.; Sahebkar, A.; Östlundh, L.; Al-Rifai, R.H.; Atkin, S.L.; Sathyapalan, T. The Effect of Thiazolidinediones in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Adv. Ther. 2024, 41, 2168–2195, doi:10.1007/s12325-024-02848-3.
178. Tso, L.O.; Costello, M.F.; Albuquerque, L.E.T.; Andriolo, R.B.; Macedo, C.R. Metformin Treatment before and during IVF or ICSI in Women with Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2020, 12, CD006105, doi:10.1002/14651858.CD006105.pub4.
179. Kim, C.H.; Chon, S.J.; Lee, S.H. Effects of Lifestyle Modification in Polycystic Ovary Syndrome Compared to Metformin Only or Metformin Addition: A Systematic Review and Meta-Analysis. Sci. Rep. 2020, 10, 7802, doi:10.1038/s41598-020-64776-w.
180. Abu Hashim, H.; Foda, O.; Ghayaty, E. Combined Metformin-Clomiphene in Clomiphene-Resistant Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Acta Obstet. Gynecol. Scand. 2015, 94, 921–930, doi:10.1111/aogs.12673.
181. Kar, S.; Sanchita, S. Clomiphene Citrate, Metformin or a Combination of Both as the First Line Ovulation Induction Drug for Asian Indian Women with Polycystic Ovarian Syndrome: A Randomized Controlled Trial. J. Hum. Reprod. Sci. 2015, 8, 197–201, doi:10.4103/0974-1208.170373.
182. Begum, M.R.; Akhter, S.; Ehsan, M.; Begum, M.S.; Khan, F. Pretreatment and Co-Administration of Oral Anti-Diabetic Agent with Clomiphene Citrate or rFSH for Ovulation Induction in Clomiphene-Citrate-Resistant Polycystic Ovary Syndrome: Pretreatment and Co-Administration. J. Obstet. Gynaecol. Res. 2013, 39, 966–973, doi:10.1111/j.1447-0756.2012.02072.x.
183. Zhao, H.; Zhang, J.; Xing, C.; Cheng, X.; He, B. Metformin versus Metformin plus Pioglitazone on Gonadal and Metabolic Profiles in Normal-Weight Women with Polycystic Ovary Syndrome: A Single-Center, Open-Labeled Prospective Randomized Controlled Trial. J. Ovarian Res. 2024, 17, doi:10.1186/s13048-024-01367-7.
184. Hu, Y.; Song, X.; Hamiti, S.; Ma, Y.; Yusufu, M.; Wang, X.; Zhang, K.; Guo, Y. Comparison of Exenatide Alone or Combined with Metformin versus Metformin in the Treatment of Polycystic Ovaries: A Systematic Review and Meta-Analysis. BMC Endocr. Disord. 2023, 23, 250, doi:10.1186/s12902-023-01497-x.
185. Ye, Z.-R.; Yan, C.-Q.; Liao, N.; Wen, S.-H. The Effectiveness and Safety of Exenatide versus Metformin in Patients with Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. Reprod. Sci. 2023, 30, 2349–2361, doi:10.1007/s43032-023-01222-y.
186. Jensterle, M.; Janez, A.; Fliers, E.; DeVries, J.H.; Vrtacnik-Bokal, E.; Siegelaar, S.E. The Role of Glucagon-like Peptide-1 in Reproduction: From Physiology to Therapeutic Perspective. Hum. Reprod. Update 2019, 25, 504–517, doi:10.1093/humupd/dmz019.
187. Cena, H.; Chiovato, L.; Nappi, R.E. Obesity, Polycystic Ovary Syndrome, and Infertility: A New Avenue for GLP-1 Receptor Agonists. J. Clin. Endocrinol. Metab. 2020, 105, e2695–e2709, doi:10.1210/clinem/dgaa285.
188. Jensterle, M.; Herman, R.; Janež, A. Therapeutic Potential of Glucagon-like Peptide-1 Agonists in Polycystic Ovary Syndrome: From Current Clinical Evidence to Future Perspectives. Biomedicines 2022, 10, 1989, doi:10.3390/biomedicines10081989.
189. Vyrides, A.A.; El Mahdi, E.; Giannakou, K. Ovulation Induction Techniques in Women with Polycystic Ovary Syndrome. Front. Med. (Lausanne) 2022, 9, 982230, doi:10.3389/fmed.2022.982230.

190. Franik, S.; Le, Q.-K.; Kremer, J.A.; Kiesel, L.; Farquhar, C. Aromatase Inhibitors (Letrozole) for Ovulation Induction in Infertile Women with Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2022, 9, CD010287, doi:10.1002/14651858.CD010287.pub4.
191. Phillips, K.; Olanrewaju, R.A.; Omole, F. Infertility: Evaluation and Management. Am. Fam. Physician 2023, 107, 623–630.
192. Dai, M.; Hong, L.; Yin, T.; Liu, S. Disturbed Follicular Microenvironment in Polycystic Ovary Syndrome: Relationship to Oocyte Quality and Infertility. Endocrinology 2024, 165, doi:10.1210/endocr/bqae023.
193. Von Hofe, J.; Bates, G.W. Ovulation Induction. Obstet. Gynecol. Clin. North Am. 2015, 42, 27–37, doi:10.1016/j.ogc.2014.09.007.
194. Gadalla, M.A.; Huang, S.; Wang, R.; Norman, R.J.; Abdullah, S.A.; El Saman, A.M.; Ismail, A.M.; van Wely, M.; Mol, B.W.J. Effect of Clomiphene Citrate on Endometrial Thickness, Ovulation, Pregnancy and Live Birth in Anovulatory Women: Systematic Review and Meta-analysis. Ultrasound Obstet. Gynecol. 2018, 51, 64–76, doi:10.1002/uog.18933.
195. Gorlitsky, G.A.; Kase, N.G.; Speroff, L. Ovulation and Pregnancy Rates with Clomiphene Citrate. Obstet. Gynecol. 1978, 51, 265–269, doi:10.1097/00006250-197803000-00002.
196. Gysler, M.; March, C.M.; Mishell, D.R., Jr; Bailey, E.J. A Decade's Experience with an Individualized Clomiphene Treatment Regimen Including Its Effect on the Postcoital Test. Fertil. Steril. 1982, 37, 161–167, doi:10.1016/s0015-0282(16)46033-4.
197. Kousta, E.; White, D.M.; Franks, S. Modern Use of Clomiphene Citrate in Induction of Ovulation. Hum. Reprod. Update 1997, 3, 359–365, doi:10.1093/humupd/3.4.359.
198. Huppert, L.C. Induction of Ovulation with Clomiphene Citrate. Fertil. Steril. 1979, 31, 1–8, doi:10.1016/s0015-0282(16)43749-0.
199. Peng, G.; Yan, Z.; Liu, Y.; Li, J.; Ma, J.; Tong, N.; Wang, Y. The Effects of First-Line Pharmacological Treatments for Reproductive Outcomes in Infertile Women with PCOS: A Systematic Review and Network Meta-Analysis. Reprod. Biol. Endocrinol. 2023, 21, 24, doi:10.1186/s12958-023-01075-9.
200. Weiss, N.S.; Kostova, E.; Nahuis, M.; Mol, B.W.J.; van der Veen, F.; van Wely, M. Gonadotrophins for Ovulation Induction in Women with Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2019, 1, CD010290, doi:10.1002/14651858.CD010290.pub3.
201. Bayram, N.; van Wely, M.; van Der Veen, F. Recombinant FSH versus Urinary Gonadotrophins or Recombinant FSH for Ovulation Induction in Subfertility Associated with Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2001, CD002121, doi:10.1002/14651858.CD002121.
202. Liu, Z.; Geng, Y.; Huang, Y.; Hu, R.; Li, F.; Song, Y.; Zhang, M. Letrozole Compared with Clomiphene Citrate for Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis: A Systematic Review and Meta-Analysis. Obstet. Gynecol. 2023, 141, 523–534, doi:10.1097/AOG.0000000000005070.
203. Mandelbaum, R.S.; Agarwal, R.; Melville, S.; Violette, C.J.; Winer, S.; Shoupe, D.; Matsuo, K.; Paulson, R.J.; Quinn, M.M. A Comparison of Letrozole Regimens for Ovulation Induction in Women with Polycystic Ovary Syndrome. F S Rep. 2024, 5, 170–175, doi:10.1016/j.xfre.2024.03.004.
204. Abu-Zaid, A.; Gari, A.; Sabban, H.; Alshahrani, M.S.; Khadawardi, K.; Badghish, E.; AlSghan, R.; Bukhari, I.A.; Alyousef, A.; Abuzaid, M.; et al. Comparison of Letrozole and Clomiphene Citrate in Pregnancy Outcomes in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Reprod. Sci. 2024, 31, 883–905, doi:10.1007/s43032-023-01404-8.
205. Zhang, Y.; Zhang, C.; Shu, J.; Guo, J.; Chang, H.-M.; Leung, P.C.K.; Sheng, J.-Z.; Huang, H. Adjuvant Treatment Strategies in Ovarian Stimulation for Poor Responders Undergoing IVF: A Systematic Review and Network Meta-Analysis. Hum. Reprod. Update 2020, 26, 247–263, doi:10.1093/humupd/dmz046.
206. Ashkar, A.; Jadoon, B.; Ali Baig, M.M.; Irfan, S.A.; El-Gayar, M.; Siddiqui, F.Z. Is Combined Letrozole and Clomiphene Superior to Either as Monotherapy: A Systemic Review and Meta-Analysis Based on Clinical Trials. Gynecol. Endocrinol. 2024, 40, 2405114, doi:10.1080/09513590.2024.2405114.
207. Stein, I.F.; Leventhal, M.L. Amenorrhea Associated with Bilateral Polycystic Ovaries. Am. J. Obstet. Gynecol. 1935, 29, 181–191, doi:10.1016/s0002-9378(15)30642-6.
208. Lebbi, I.; Ben Temime, R.; Fadhlaoui, A.; Feki, A. Ovarian Drilling in PCOS: Is It Really Useful? Front. Surg. 2015, 2, 30, doi:10.3389/fsurg.2015.00030.

209. Seow, K.-M.; Chang, Y.-W.; Chen, K.-H.; Juan, C.-C.; Huang, C.-Y.; Lin, L.-T.; Tsui, K.-H.; Chen, Y.-J.; Lee, W.-L.; Wang, P.-H. Molecular Mechanisms of Laparoscopic Ovarian Drilling and Its Therapeutic Effects in Polycystic Ovary Syndrome. Int. J. Mol. Sci. 2020, 21, 8147, doi:10.3390/ijms21218147.
210. Gjönnaess, H. Polycystic Ovarian Syndrome Treated by Ovarian Electrocautery through the Laparoscope. Fertil. Steril. 1984, 41, 20–25, doi:10.1016/s0015-0282(16)47534-5.
211. Abu Hashim, H. Predictors of Success of Laparoscopic Ovarian Drilling in Women with Polycystic Ovary Syndrome: An Evidence-Based Approach. Arch. Gynecol. Obstet. 2015, 291, 11–18, doi:10.1007/s00404-014-3447-6.
212. Nayak, P.; Agrawal, S.; Mitra, S. Laparoscopic Ovarian Drilling: An Alternative but Not the Ultimate in the Management of Polycystic Ovary Syndrome. J. Nat. Sci. Biol. Med. 2015, 6, 40, doi:10.4103/0976-9668.149076.
213. Bordewijk, E.M.; Ng, K.Y.B.; Rakic, L.; Mol, B.W.J.; Brown, J.; Crawford, T.J.; van Wely, M. Laparoscopic Ovarian Drilling for Ovulation Induction in Women with Anovulatory Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2020, 2, CD001122, doi:10.1002/14651858.CD001122.pub5.
214. DiNicolantonio, J.J.; H O'Keefe, J. Myo-Inositol for Insulin Resistance, Metabolic Syndrome, Polycystic Ovary Syndrome and Gestational Diabetes. Open Heart 2022, 9, e001989, doi:10.1136/openhrt-2022-001989.
215. Unfer, V.; Porcaro, G. Updates on the Myo-Inositol plus D-Chiro-Inositol Combined Therapy in Polycystic Ovary Syndrome. Expert Rev. Clin. Pharmacol. 2014, 7, 623–631, doi:10.1586/17512433.2014.925795.
216. Genazzani, A.D. Inositol as Putative Integrative Treatment for PCOS. Reprod. Biomed. Online 2016, 33, 770–780, doi:10.1016/j.rbmo.2016.08.024.
217. Bizzarri, M.; Carlomagno, G. Inositol: History of an Effective Therapy for Polycystic Ovary Syndrome. Eur. Rev. Med. Pharmacol. Sci. 2014, 18, 1896–1903.
218. Dinicola, S.; Chiu, T.T.Y.; Unfer, V.; Carlomagno, G.; Bizzarri, M. The Rationale of the Myo-Inositol and D-Chiro-Inositol Combined Treatment for Polycystic Ovary Syndrome: The Journal of Clinical Pharmacology. J. Clin. Pharmacol. 2014, 54, 1079–1092, doi:10.1002/jcph.362.
219. Greff, D.; Juhász, A.E.; Váncsa, S.; Váradi, A.; Sipos, Z.; Szinte, J.; Park, S.; Hegyi, P.; Nyirády, P.; Ács, N.; et al. Inositol Is an Effective and Safe Treatment in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Reprod. Biol. Endocrinol. 2023, 21, 10, doi:10.1186/s12958-023-01055-z.
220. Fitz, V.; Graca, S.; Mahalingaiah, S.; Liu, J.; Lai, L.; Butt, A.; Armour, M.; Rao, V.; Naidoo, D.; Maunder, A.; et al. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis to Inform the 2023 Update of the International Evidence-Based PCOS Guidelines. J. Clin. Endocrinol. Metab. 2024, 109, 1630–1655, doi:10.1210/clinem/dgad762.
221. Benavides-Aguilar, J.A.; Torres-Copado, A.; Isidoro-Sánchez, J.; Pathak, S.; Duttaroy, A.K.; Banerjee, A.; Paul, S. The Regulatory Role of MicroRNAs in Obesity and Obesity-Derived Ailments. Genes (Basel) 2023, 14, 2070, doi:10.3390/genes14112070.
222. Murri, M.; Insenser, M.; Fernández-Durán, E.; San-Millán, J.L.; Luque-Ramírez, M.; Escobar-Morreale, H.F. Non-Targeted Profiling of Circulating microRNAs in Women with Polycystic Ovary Syndrome (PCOS): Effects of Obesity and Sex Hormones. Metabolism 2018, 86, 49–60, doi:10.1016/j.metabol.2018.01.011.
223. Chen, B.; Xu, P.; Wang, J.; Zhang, C. The Role of MiRNA in Polycystic Ovary Syndrome (PCOS). Gene 2019, 706, 91–96, doi:10.1016/j.gene.2019.04.082.
224. Insenser, M.; Quintero, A.; de Lope, S.; Álvarez-Blasco, F.; Martínez-García, M.Á.; Luque-Ramírez, M.; Escobar-Morreale, H.F. Validation of Circulating microRNAs miR-142-3p and miR-598-3p in Women with Polycystic Ovary Syndrome as Potential Diagnostic Markers. Hum. Reprod. 2023, 38, 951–960, doi:10.1093/humrep/dead043.
225. Zhang, F.; Li, S.-P.; Zhang, T.; Yu, B.; Zhang, J.; Ding, H.-G.; Ye, F.-J.; Yuan, H.; Ma, Y.-Y.; Pan, H.-T.; et al. High Throughput microRNAs Sequencing Profile of Serum Exosomes in Women with and without Polycystic Ovarian Syndrome. PeerJ 2021, 9, e10998, doi:10.7717/peerj.10998.
226. Abdalla, M.; Deshmukh, H.; Atkin, S.L.; Sathyapalan, T. miRNAs as a Novel Clinical Biomarker and Therapeutic Targets in Polycystic Ovary Syndrome (PCOS): A Review. Life Sci. 2020, 259, 118174, doi:10.1016/j.lfs.2020.118174.

227. Mu, L.; Sun, X.; Tu, M.; Zhang, D. Non-Coding RNAs in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Reprod. Biol. Endocrinol. 2021, 19, 10, doi:10.1186/s12958-020-00687-9.
228. Mao, Z.; Li, T.; Zhao, H.; Qin, Y.; Wang, X.; Kang, Y. Identification of Epigenetic Interactions between microRNA and DNA Methylation Associated with Polycystic Ovarian Syndrome. J. Hum. Genet. 2021, 66, 123–137, doi:10.1038/s10038-020-0819-6.
229. Xuan, X.; Zhang, L.; Tian, C.; Wu, T.; Ye, H.; Cao, J.; Chen, F.; Liang, Y.; Yang, H.; Huang, C. Interleukin-22 and Connective Tissue Diseases: Emerging Role in Pathogenesis and Therapy. Cell Biosci. 2021, 11, 2, doi:10.1186/s13578-020-00504-1.
230. Seth, P.; Dubey, S. IL-22 as a Target for Therapeutic Intervention: Current Knowledge on Its Role in Various Diseases. Cytokine 2023, 169, 156293, doi:10.1016/j.cyto.2023.156293.
231. Qi, X.; Yun, C.; Liao, B.; Qiao, J.; Pang, Y. The Therapeutic Effect of Interleukin-22 in High Androgen-Induced Polycystic Ovary Syndrome. J. Endocrinol. 2020, 245, 281–289, doi:10.1530/JOE-19-0589.
232. Geng, Y.; Liu, Z.; Hu, R.; Ma, W.; Wu, X.; Dong, H.; Song, K.; Xu, X.; Huang, Y.; Li, F.; et al. Opportunities and Challenges: Interleukin-22 Comprehensively Regulates Polycystic Ovary Syndrome from Metabolic and Immune Aspects. J. Ovarian Res. 2023, 16, 149, doi:10.1186/s13048-023-01236-9.
233. Aksun, S.; Ersal, E.; Portakal, O.; Yildiz, B.O. Interleukin-22/Interleukin-22 Binding Protein Axis and Oral Contraceptive Use in Polycystic Ovary Syndrome. Endocrine 2023, 81, 54–57, doi:10.1007/s12020-023-03360-4.
234. Chen, W.; Liao, B.; Yun, C.; Zhao, M.; Pang, Y. Interlukin-22 Improves Ovarian Function in Polycystic Ovary Syndrome Independent of Metabolic Regulation: A Mouse-Based Experimental Study. J. Ovarian Res. 2024, 17, 100, doi:10.1186/s13048-024-01428-x.
235. Liu, L.; Li, X.; Chen, Y.; Li, Y.Z.; Liu, Z.; Duan, Y.; Chen, Y. Interleukin-22 Promotes Proliferation and Reverses LPS-Induced Apoptosis and Steroidogenesis Attenuation in Human Ovarian Granulosa Cells: Implications for Polycystic Ovary Syndrome Pathogenesis. J. Matern. Fetal. Neonatal Med. 2023, 36, 2253347, doi:10.1080/14767058.2023.2253347.
236. Lal, S.; Sayeed Akhtar, M.; Faiyaz Khan, M.; Aldosari, S.A.; Mukherjee, M.; Sharma, A.K. Molecular Basis of Phytochemical-Gut Microbiota Interactions. Drug Discov. Today 2023, 28, 103824, doi:10.1016/j.drudis.2023.103824.
237. Yurtdaş, G.; Akdevelioğlu, Y. A New Approach to Polycystic Ovary Syndrome: The Gut Microbiota. J. Am. Coll. Nutr. 2020, 39, 371–382, doi:10.1080/07315724.2019.1657515.
238. Liu, J.; Liu, Y.; Li, X. Effects of Intestinal Flora on Polycystic Ovary Syndrome. Front. Endocrinol. (Lausanne) 2023, 14, doi:10.3389/fendo.2023.1151723.
239. Angoorani, P.; Ejtahed, H.-S.; Ettehad Marvasti, F.; Taghavi, M.; Mohammadpour Ahranjani, B.; Hasani-Ranjbar, S.; Larijani, B. The Effects of Probiotics, Prebiotics, and Synbiotics on Polycystic Ovarian Syndrome: An Overview of Systematic Reviews. Front. Med. (Lausanne) 2023, 10, doi:10.3389/fmed.2023.1141355.
240. Zhang, M.; Hu, R.; Huang, Y.; Zhou, F.; Li, F.; Liu, Z.; Geng, Y.; Dong, H.; Ma, W.; Song, K.; et al. Present and Future: Crosstalks between Polycystic Ovary Syndrome and Gut Metabolites Relating to Gut Microbiota. Front. Endocrinol. (Lausanne) 2022, 13, doi:10.3389/fendo.2022.933110.
241. Feng, T.; Wang, J. Oxidative Stress Tolerance and Antioxidant Capacity of Lactic Acid Bacteria as Probiotic: A Systematic Review. Gut Microbes 2020, 12, 1801944, doi:10.1080/19490976.2020.1801944.
242. Yang, K.M.; Kim, J.-S.; Kim, H.-S.; Kim, Y.-Y.; Oh, J.-K.; Jung, H.-W.; Park, D.-S.; Bae, K.-H. Lactobacillus Reuteri AN417 Cell-Free Culture Supernatant as a Novel Antibacterial Agent Targeting Oral Pathogenic Bacteria. Sci. Rep. 2021, 11, doi:10.1038/s41598-020-80921-x.
243. Liu, Y.-C.; Wu, C.-R.; Huang, T.-W. Preventive Effect of Probiotics on Oral Mucositis Induced by Cancer Treatment: A Systematic Review and Meta-Analysis. Int. J. Mol. Sci. 2022, 23, 13268, doi:10.3390/ijms232113268.
244. Zhao, M.; Chu, J.; Feng, S.; Guo, C.; Xue, B.; He, K.; Li, L. Immunological Mechanisms of Inflammatory Diseases Caused by Gut Microbiota Dysbiosis: A Review. Biomed. Pharmacother. 2023, 164, 114985, doi:10.1016/j.biopha.2023.114985.

245. Hou, K.; Wu, Z.-X.; Chen, X.-Y.; Wang, J.-Q.; Zhang, D.; Xiao, C.; Zhu, D.; Koya, J.B.; Wei, L.; Li, J.; et al. Microbiota in Health and Diseases. Signal Transduct. Target. Ther. 2022, 7, doi:10.1038/s41392-022-00974-4.
246. Guo, H.; Luo, J.; Lin, H. Exploration of the Pathogenesis of Polycystic Ovary Syndrome Based on Gut Microbiota: A Review. Medicine (Baltimore) 2023, 102, e36075, doi:10.1097/md.0000000000036075.
247. Tabrizi, R.; Ostadmohammadi, V.; Akbari, M.; Lankarani, K.B.; Vakili, S.; Peymani, P.; Karamali, M.; Kolahdooz, F.; Asemi, Z. The Effects of Probiotic Supplementation on Clinical Symptom, Weight Loss, Glycemic Control, Lipid and Hormonal Profiles, Biomarkers of Inflammation, and Oxidative Stress in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Probiotics Antimicrob. Proteins 2022, 14, 1–14, doi:10.1007/s12602-019-09559-0.
248. Sun, Y.; Gao, S.; Ye, C.; Zhao, W. Gut Microbiota Dysbiosis in Polycystic Ovary Syndrome: Mechanisms of Progression and Clinical Applications. Front. Cell. Infect. Microbiol. 2023, 13, doi:10.3389/fcimb.2023.1142041.
249. American Society of Microbiology Fecal Microbiota Transplants (FMT): Past, Present and Future Available online: https://asm.org/articles/2024/february/fecal-microbiota-transplants-past-present-future (accessed on 25 December 2024).
250. Zecheng, L.; Donghai, L.; Runchuan, G.; Yuan, Q.; Qi, J.; Yijia, Z.; Shuaman, R.; Xiaoqi, L.; Yi, W.; Ni, M.; et al. Fecal Microbiota Transplantation in Obesity Metabolism: A Meta Analysis and Systematic Review. Diabetes Res. Clin. Pract. 2023, 202, 110803, doi:10.1016/j.diabres.2023.110803.
251. Tariq, R.; Syed, T.; Yadav, D.; Prokop, L.J.; Singh, S.; Loftus, E.V.; Pardi, D.S.; Khanna, S. Outcomes of Fecal Microbiota Transplantation for C. Difficile Infection in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. J. Clin. Gastroenterol. 2023, 57, 285–293, doi:10.1097/mcg.0000000000001633.
252. Yang, Y.; Cheng, J.; Liu, C.; Zhang, X.; Ma, N.; Zhou, Z.; Lu, W.; Wu, C. Gut Microbiota in Women with Polycystic Ovary Syndrome: An Individual Based Analysis of Publicly Available Data. EClinicalMedicine 2024, 77, 102884, doi:10.1016/j.eclinm.2024.102884.
253. Moadi, L.; Turjeman, S.; Asulin, N.; Koren, O. The Effect of Testosterone on the Gut Microbiome in Mice. Commun. Biol. 2024, 7, doi:10.1038/s42003-024-06470-5.
254. Chen, K.; Geng, H.; Ye, C.; Liu, J. Dysbiotic Alteration in the Fecal Microbiota of Patients with Polycystic Ovary Syndrome. Microbiol. Spectr. 2024, 12, doi:10.1128/spectrum.04291-23.
255. Yang, Y.; Yan, J.; Li, S.; Liu, M.; Han, R.; Wang, Y.; Wang, Z.; Wang, D. Efficacy of Fecal Microbiota Transplantation in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Endocrine 2023, 84, 48–62, doi:10.1007/s12020-023-03606-1.
256. Chen, J.; Huang, C.; Zhang, T.; Gong, W.; Deng, X.; Liu, H.; Liu, J.; Guo, Y. The Effects of Statins on Hyperandrogenism in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Reprod. Biol. Endocrinol. 2021, 19, doi:10.1186/s12958-021-00863-5.
257. Stamerra, C.A.; Di Giosia, P.; Ferri, C.; Giorgini, P.; Reiner, Z.; Johnston, T.P.; Sahebkar, A. Statin Therapy and Sex Hormones. Eur. J. Pharmacol. 2021, 890, 173745, doi:10.1016/j.ejphar.2020.173745.
258. Kolnikaj, T.S.; Herman, R.; Janež, A.; Jensterle, M. The Current and Emerging Role of Statins in the Treatment of PCOS: The Evidence to Date. Medicina (Kaunas) 2024, 60, 244, doi:10.3390/medicina60020244.
259. Cassidy-Vu, L.; Joe, E.; Kirk, J.K. Role of Statin Drugs for Polycystic Ovary Syndrome. J. Family Reprod. Health 2016, 10, 165–175.
260. Shawish, M.I.; Bagheri, B.; Musini, V.M.; Adams, S.P.; Wright, J.M. Effect of Atorvastatin on Testosterone Levels. Cochrane Database Syst. Rev. 2021, 1, CD013211, doi:10.1002/14651858.CD013211.pub2.
261. Meng, J.; Zhu, Y. Efficacy of Simvastatin plus Metformin for Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. Eur. J. Obstet. Gynecol. Reprod. Biol. 2021, 257, 19–24, doi:10.1016/j.ejogrb.2020.11.070.
262. Mu, Y.; Cheng, D.; Yin, T.-L.; Yang, J. Vitamin D and Polycystic Ovary Syndrome: A Narrative Review. Reprod. Sci. 2021, 28, 2110–2117, doi:10.1007/s43032-020-00369-2.
263. Akbari, M.; Ostadmohammadi, V.; Lankarani, K.B.; Tabrizi, R.; Kolahdooz, F.; Heydari, S.T.; Kavari, S.H.; Mirhosseini, N.; Mafi, A.; Dastorani, M.; et al. The Effects of Vitamin D Supplementation on Biomarkers of Inflammation and Oxidative Stress among Women with Polycystic Ovary Syndrome: A Systematic Review

and Meta-Analysis of Randomized Controlled Trials. Horm. Metab. Res. 2018, 50, 271–279, doi:10.1055/s-0044-101355.

264. Trummer, C.; Schwetz, V.; Kollmann, M.; Wölfler, M.; Münzker, J.; Pieber, T.R.; Pilz, S.; Heijboer, A.C.; Obermayer-Pietsch, B.; Lerchbaum, E. Effects of Vitamin D Supplementation on Metabolic and Endocrine Parameters in PCOS: A Randomized-Controlled Trial. Eur. J. Nutr. 2019, 58, 2019–2028, doi:10.1007/s00394-018-1760-8.
265. Amiri, M.; Nahidi, F.; Yarandi, R.B.; Khalili, D.; Tohidi, M.; Tehrani, F.R. Effects of Oral Contraceptives on the Quality of Life of Women with Polycystic Ovary Syndrome: A Crossover Randomized Controlled Trial. Health Qual. Life Outcomes 2020, 18, 293, doi:10.1186/s12955-020-01544-4.
266. Mathur, R.; Levin, O.; Azziz, R. Use of Ethinylestradiol/Drospirenone Combination in Patients with the Polycystic Ovary Syndrome. Ther. Clin. Risk Manag. 2008, 4, 487–492, doi:10.2147/tcrm.s6864.
267. Ruan, X.; Kubba, A.; Aguilar, A.; Mueck, A.O. Use of Cyproterone Acetate/Ethinylestradiol in Polycystic Ovary Syndrome: Rationale and Practical Aspects. Eur. J. Contracept. Reprod. Health Care 2017, 22, 183–190, doi:10.1080/13625187.2017.1317735.
268. Li, L.; Zhang, R.; Zeng, J.; Ke, H.; Peng, X.; Huang, L.; Zhang, H.; Chen, Z.; Li, T.T.; Tan, Q.; et al. Effectiveness and Safety Assessment of Drospirenone/Ethinyl Estradiol Tablet in Treatment of PCOS Patients: A Single Center, Prospective, Observational Study. BMC Womens. Health 2020, 20, 39, doi:10.1186/s12905-020-00905-x.
269. Di Carlo, C.; Gargano, V.; Sparice, S.; Tommaselli, G.A.; Bifulco, G.; Nappi, C. Effects of an Oral Contraceptive Containing Estradiol Valerate and Dienogest on Circulating Androgen Levels and Acne in Young Patients with PCOS: An Observational Preliminary Study. Gynecol. Endocrinol. 2013, 29, 1048–1050, doi:10.3109/09513590.2013.831834.
270. Menshawy, A.; Ismail, A.; Abdel-Maboud, M.; El-Din, A.A.; Elgebaly, A.; Gadelkarim, M.; Bahbah, E.I.; Abdelghany, M.F.; Samy, A.; Abbas, A.M. Effect of Chlormadinone Acetate versus Drospirenone-Containing Oral Contraceptives on the Endocrinal Features of Women with Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis of Randomized Clinical Trials. J. Gynecol. Obstet. Hum. Reprod. 2019, 48, 763–770, doi:10.1016/j.jogoh.2019.03.025.
271. Morgante, G.; Cappelli, V.; Troìa, L.; De Leo, V. Evaluation of Different Antiandrogenic Progestins on Clinical and Biochemical Variables in Polycystic Ovary Syndrome. Eur. J. Contracept. Reprod. Health Care 2020, 25, 176–181, doi:10.1080/13625187.2020.1736546.
272. Vieira, C.S.; Martins, W.P.; Fernandes, J.B.F.; Soares, G.M.; dos Reis, R.M.; de Sá, M.F.S.; Ferriani, R.A. The Effects of 2 Mg Chlormadinone Acetate/30 Mcg Ethinylestradiol, Alone or Combined with Spironolactone, on Cardiovascular Risk Markers in Women with Polycystic Ovary Syndrome. Contraception 2012, 86, 268–275, doi:10.1016/j.contraception.2011.12.011.
273. Zhang, Q.; He, S.; Meng, Y.; Yin, T.; Ming, L.; Yang, J.; Li, S. Effect of Medroxyprogesterone Acetate Dose in Progestin-Primed Ovarian Stimulation on Pregnancy Outcomes in Poor Ovarian Response Patients with Different Body Mass Index Levels. Front. Endocrinol. (Lausanne) 2024, 15, 1352522, doi:10.3389/fendo.2024.1352522.
274. Hu, A.C.; Chapman, L.W.; Mesinkovska, N.A. The Efficacy and Use of Finasteride in Women: A Systematic Review. Int. J. Dermatol. 2019, 58, 759–776, doi:10.1111/ijd.14370.
275. Ganie, M.A.; Khurana, M.L.; Nisar, S.; Shah, P.A.; Shah, Z.A.; Kulshrestha, B.; Gupta, N.; Zargar, M.A.; Wani, T.A.; Mudasir, S.; et al. Improved Efficacy of Low-Dose Spironolactone and Metformin Combination than Either Drug Alone in the Management of Women with Polycystic Ovary Syndrome (PCOS): A Six-Month, Open-Label Randomized Study. J. Clin. Endocrinol. Metab. 2013, 98, 3599–3607, doi:10.1210/jc.2013-1040.
276. Adeyanju, O.A.; Falodun, T.O.; Fabunmi, O.A.; Olatunji, L.A.; Soladoye, A.O. Very Low Dose Spironolactone Protects Experimentally-Induced Polycystic Ovarian Syndrome from Insulin-Resistant Metabolic Disturbances by Suppressing Elevated Circulating Testosterone. Chem. Biol. Interact. 2019, 310, 108742, doi:10.1016/j.cbi.2019.108742.
277. Dhaliwal, L.K.; Suri, V.; Gupta, K.R.; Sahdev, S. Tamoxifen: An Alternative to Clomiphene in Women with Polycystic Ovary Syndrome. J. Hum. Reprod. Sci. 2011, 4, 76–79, doi:10.4103/0974-1208.86085.

278. Brown, J.; Farquhar, C. Clomiphene and Other Antioestrogens for Ovulation Induction in Polycystic Ovarian Syndrome. Cochrane Database Syst. Rev. 2016, 12, CD002249, doi:10.1002/14651858.CD002249.pub5.
279. Franik, S.; Eltrop, S.M.; Kremer, J.A.; Kiesel, L.; Farquhar, C. Aromatase Inhibitors (Letrozole) for Subfertile Women with Polycystic Ovary Syndrome. Cochrane Database Syst. Rev. 2018, 5, CD010287, doi:10.1002/14651858.CD010287.pub3.
280. Shi, S.; Hong, T.; Jiang, F.; Zhuang, Y.; Chen, L.; Huang, X. Letrozole and Human Menopausal Gonadotropin for Ovulation Induction in Clomiphene Resistance Polycystic Ovary Syndrome Patients: A Randomized Controlled Study: A Randomized Controlled Study. Medicine (Baltimore) 2020, 99, e18383, doi:10.1097/MD.0000000000018383.
281. Andoh, K.; Mizunuma, H.; Liu, X.; Kamijo, T.; Yamada, K.; Ibuki, Y. A Comparative Study of Fixed-Dose, Step-down, and Low-Dose Step-up Regimens of Human Menopausal Gonadotropin for Patients with Polycystic Ovary Syndrome. Fertil. Steril. 1998, 70, 840–846, doi:10.1016/s0015-0282(98)00308-2.
282. Ho, J. Patient Education: In Vitro Fertilization (IVF) (Beyond the Basics) Available online: https://www.uptodate.com/contents/in-vitro-fertilization-ivf-beyond-the-basics/print (accessed on 26 December 2024).
283. Olivennes, F.; Howies, C.M.; Borini, A.; Germond, M.; Trew, G.; Wikland, M.; Zegers-Hochschild, F.; Saunders, H.; Alam, V. Individualizing FSH Dose for Assisted Reproduction Using a Novel Algorithm: The CONSORT Study. Reprod. Biomed. Online 2011, 22, S73–S82, doi:10.1016/s1472-6483(11)60012-6.
284. Ghanem, M.E.; Elboghdady, L.A.; Hassan, M.; Helal, A.S.; Gibreel, A.; Houssen, M.; Shaker, M.E.; Bahlol, I.; Mesbah, Y. Clomiphene Citrate Co-Treatment with Low Dose Urinary FSH versus Urinary FSH for Clomiphene Resistant PCOS: Randomized Controlled Trial. J. Assist. Reprod. Genet. 2013, 30, 1477–1485, doi:10.1007/s10815-013-0090-2.
285. Medscape. Gonal-f, Gonal-f RFF (Follitropin Alfa) Dosing, Indications, Interactions, Adverse Effects, and More Available online: https://reference.medscape.com/drug/gonal-f-rff-follitropin-alfa-342804 (accessed on 26 December 2024).
286. Medscape. Follistim AQ (Follitropin Beta) Dosing, Indications, Interactions, Adverse Effects, and More Available online: https://reference.medscape.com/drug/follistim-aq-follitropin-beta-999524?_gl=1*q3mixz*_gcl_au*MTg3MzExOTQzMC4xNzM0NTk0OTk3 (accessed on 26 December 2024).
287. Arya, S.; Hansen, K.R.; Wild, R.A. Metformin, Rosiglitazone, or Both for Obese Women with Polycystic Ovary Syndrome? Fertil. Steril. 2020, 113, 87–88, doi:10.1016/j.fertnstert.2019.10.006.
288. Li, Y.; Tan, J.; Wang, Q.; Duan, C.; Hu, Y.; Huang, W. Comparing the Individual Effects of Metformin and Rosiglitazone and Their Combination in Obese Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. Fertil. Steril. 2020, 113, 197–204, doi:10.1016/j.fertnstert.2019.09.011.
289. Morley, L.C.; Tang, T.; Yasmin, E.; Norman, R.J.; Balen, A.H. Insulin-Sensitising Drugs (Metformin, Rosiglitazone, Pioglitazone, D-Chiro-Inositol) for Women with Polycystic Ovary Syndrome, Oligo Amenorrhoea and Subfertility. Cochrane Database Syst. Rev. 2017, 11, CD003053, doi:10.1002/14651858.CD003053.pub6.
290. Koo, Y.-A.; Shin, S.-Y.; Yoon, B.-K.; Choi, D. Pioglitazone for Treating Polycystic Ovary Syndrome in Non-Obese Women of Reproductive Age with Different Clinical Presentations. Gynecol. Endocrinol. 2007, 23, 461–467, doi:10.1080/09513590701492689.
291. Azziz, R.; Ehrmann, D.; Legro, R.S.; Whitcomb, R.W.; Hanley, R.; Fereshetian, A.G.; O'Keefe, M.; Ghazzi, M.N.; PCOS/Troglitazone Study Group Troglitazone Improves Ovulation and Hirsutism in the Polycystic Ovary Syndrome: A Multicenter, Double Blind, Placebo-Controlled Trial. J. Clin. Endocrinol. Metab. 2001, 86, 1626–1632, doi:10.1210/jcem.86.4.7375.
292. Javed, Z.; Papageorgiou, M.; Deshmukh, H.; Rigby, A.S.; Qamar, U.; Abbas, J.; Khan, A.Y.; Kilpatrick, E.S.; Atkin, S.L.; Sathyapalan, T. Effects of Empagliflozin on Metabolic Parameters in Polycystic Ovary Syndrome: A Randomized Controlled Study. Clin. Endocrinol. (Oxf.) 2019, 90, 805–813, doi:10.1111/cen.13968.

293. Javed, Z.; Papageorgiou, M.; Madden, L.A.; Rigby, A.S.; Kilpatrick, E.S.; Atkin, S.L.; Sathyapalan, T. The Effects of Empagliflozin vs Metformin on Endothelial Microparticles in Overweight/Obese Women with Polycystic Ovary Syndrome. Endocr. Connect. 2020, 9, 563–569, doi:10.1530/ec-20-0173.
294. Sinha, B.; Ghosal, S. A Meta-Analysis of the Effect of Sodium Glucose Cotransporter-2 Inhibitors on Metabolic Parameters in Patients with Polycystic Ovary Syndrome. Front. Endocrinol. (Lausanne) 2022, 13, 830401, doi:10.3389/fendo.2022.830401.
295. Elkind-Hirsch, K.E.; Chappell, N.; Seidemann, E.; Storment, J.; Bellanger, D. Exenatide, Dapagliflozin, or Phentermine/Topiramate Differentially Affect Metabolic Profiles in Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 2021, 106, 3019–3033, doi:10.1210/clinem/dgab408.
296. Daneshjou, D.; Soleimani Mehranjani, M.; Zadeh Modarres, S.; Shariatzadeh, M.A. Sitagliptin/Metformin: A New Medical Treatment in Polycystic Ovary Syndrome. Trends Endocrinol. Metab. 2020, 31, 890–892, doi:10.1016/j.tem.2020.09.002.
297. Devin, J.K.; Nian, H.; Celedonio, J.E.; Wright, P.; Brown, N.J. Sitagliptin Decreases Visceral Fat and Blood Glucose in Women with Polycystic Ovarian Syndrome. J. Clin. Endocrinol. Metab. 2020, 105, 136–151, doi:10.1210/clinem/dgz028.
298. Zhang, L.; Chen, A.; Lu, J.; Ren, L.; Hu, Z. Effects of Sitagliptin on Metabolic Indices and Hormone Levels in Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. Reprod. Sci. 2023, 30, 1065–1073, doi:10.1007/s43032-022-01061-3.
299. Nylander, M.; Frøssing, S.; Clausen, H.V.; Kistorp, C.; Faber, J.; Skouby, S.O. Effects of Liraglutide on Ovarian Dysfunction in Polycystic Ovary Syndrome: A Randomized Clinical Trial. Reprod. Biomed. Online 2017, 35, 121–127, doi:10.1016/j.rbmo.2017.03.023.
300. Nylander, M.; Frøssing, S.; Kistorp, C.; Faber, J.; Skouby, S.O. Liraglutide in Polycystic Ovary Syndrome: A Randomized Trial, Investigating Effects on Thrombogenic Potential. Endocr. Connect. 2017, 6, 89–99, doi:10.1530/EC-16-0113.
301. Elkind-Hirsch, K.E.; Chappell, N.; Shaler, D.; Storment, J.; Bellanger, D. Liraglutide 3 Mg on Weight, Body Composition, and Hormonal and Metabolic Parameters in Women with Obesity and Polycystic Ovary Syndrome: A Randomized Placebo-Controlled-Phase 3 Study. Fertil. Steril. 2022, 118, 371–381, doi:10.1016/j.fertnstert.2022.04.027.
302. Celik, O.; Acbay, O. Effects of Metformin plus Rosuvastatin on Hyperandrogenism in Polycystic Ovary Syndrome Patients with Hyperlipidemia and Impaired Glucose Tolerance. J. Endocrinol. Invest. 2012, 35, 905–910, doi:10.3275/8371.
303. Sathyapalan, T.; Kilpatrick, E.S.; Coady, A.-M.; Atkin, S.L. The Effect of Atorvastatin in Patients with Polycystic Ovary Syndrome: A Randomized Double-Blind Placebo-Controlled Study. J. Clin. Endocrinol. Metab. 2009, 94, 103–108, doi:10.1210/jc.2008-1750.
304. Gao, B.; Xiang, X. Interleukin-22 from Bench to Bedside: A Promising Drug for Epithelial Repair. Cell. Mol. Immunol. 2019, 16, 666–667, doi:10.1038/s41423-018-0055-6.
305. Liao, B.; Chen, W.; Qi, X.; Yun, C.; Pang, Y. Interleukin-22 Improves Ovulation in Polycystic Ovary Syndrome via STAT3 Signaling. Mol. Hum. Reprod. 2024, 30, doi:10.1093/molehr/gaae037.