UNIVERSITY OF PADOVA
Department of Land, Environment Agriculture and Forestry (TESAF)

Master Course in Food and Health

Study of Food Patterns among patients with Polycystic Ovary Syndrome (PCOS); Systematic Review and Meta-Analysis

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A.Y. 2023 - 2024

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ABSTRACT

Introduction- Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder affecting women of reproductive age. It is characterized by a spectrum of symptoms, including polycystic ovaries, reproductive dysfunction, metabolic imbalances, hyperandrogenism, menstrual irregularities, and obesity. The multifaceted nature of PCOS, involving genetic, environmental, and lifestyle-related factors, complicates its diagnosis and management. Understanding the impact of dietary patterns and lifestyle modifications on PCOS can provide valuable insights for effective treatment strategies.

Aim- This systematic review and meta-analysis aimed to investigate the influence of dietary patterns and lifestyle modifications on the management of PCOS symptoms and overall health outcomes in affected women.

Methods- An extensive literature search was conducted across databases such as PubMed and Scopus, which produced 102 and 126 results, respectively. This resulted in a total of 228 articles. After removing 38 duplicates using the Endnote tool, 190 studies were screened for relevance based on their titles and abstracts. A total of 137 studies were excluded for being irrelevant to the research focus. 53 articles underwent full-text examination, of which 12 met the criteria for inclusion in the qualitative analysis. Furthermore, 4 studies were included in the quantitative meta-analysis.

Results- The findings from the systematic review highlight that lifestyle modifications, particularly weight management and dietary interventions, play a significant role in the management of PCOS symptoms. Ketogenic diets and medical nutrition therapy were identified as effective dietary strategies for reducing PCOS symptoms. Additionally, the review underscored the importance of combining physical activity, mood and sleep modifications, and herbal therapies as part of a comprehensive management plan for PCOS.

The heterogeneity of PCOS poses a challenge for standardizing diagnostic criteria. Despite the use of various diagnostic frameworks, such as the Rotterdam criteria, there is a pressing need for more consistent and accurate diagnostic methods to improve patient outcomes.

Conclusion- This study provides a comprehensive overview of the role of dietary patterns and lifestyle modifications in managing PCOS. The results emphasize the necessity for personalized treatment plans that address individual symptoms and lifestyle factors. Future research should focus on longitudinal studies to better understand the long-term effects of these interventions on PCOS management. Healthcare providers are encouraged to consider these findings when developing treatment strategies, as they offer valuable guidance for improving the quality of life for women with PCOS.

RIASSUNTO

Introduzione- La sindrome dell'ovaio policistico (PCOS) è un comune disturbo endocrino che colpisce le donne in età riproduttiva. È caratterizzata da una serie di sintomi, tra cui ovaie policistiche, disfunzione riproduttiva, squilibri metabolici, iperandrogenismo, irregolarità mestruali e obesità. La natura sfaccettata della PCOS, che coinvolge fattori genetici, ambientali e legati allo stile di vita, complica la diagnosi e la gestione della malattia. Comprendere l'impatto dei modelli dietetici e delle modifiche dello stile di vita sulla PCOS può fornire preziosi spunti per strategie di trattamento efficaci.

Obiettivo- Questa revisione sistematica e meta-analisi mirava a indagare l'influenza dei modelli dietetici e delle modifiche dello stile di vita sulla gestione dei sintomi della PCOS e sui risultati complessivi sulla salute delle donne affette.

Metodi- È stata condotta una vasta ricerca bibliografica su database come PubMed e Scopus, che ha prodotto rispettivamente 102 e 126 risultati. Ciò ha portato a un totale di 228 articoli. Dopo aver rimosso 38 duplicati utilizzando lo strumento Endnote, sono stati esaminati 190 studi in base alla pertinenza dei loro titoli e abstract. Un totale di 137 studi sono stati esclusi per non essere pertinenti al focus della ricerca. 53 articoli sono stati esaminati a tutto testo, di cui 12 hanno soddisfatto i criteri per essere inclusi nell'analisi qualitativa. Inoltre, 4 studi sono stati inclusi nella meta-analisi quantitativa.

Risultati- I risultati della revisione sistematica evidenziano che le modifiche dello stile di vita, in particolare la gestione del peso e le modifiche dietetiche, giocano un ruolo significativo nella gestione dei sintomi della PCOS. Diets chetogeniche e terapie dietetiche mediche sono state identificate come strategie dietetiche efficaci per alleviare i sintomi della PCOS. Inoltre, la revisione ha sottolineato l'importanza dell'inclusione di attività fisica, modifiche dell'umore e del sonno, e terapie a base di erbe come parte di un piano di gestione completo per la PCOS.

L'eterogeneità della PCOS rappresenta una sfida per la standardizzazione dei criteri di diagnosi. Nonostante l'uso di diversi quadri diagnostici, come i criteri di Rotterdam, c'è un urgente bisogno di metodi diagnostici più consistenti e accurati per migliorare gli esiti dei pazienti.

Conclusioni- Questo studio fornisce una panoramica completa del ruolo dei modelli dietetici e delle modifiche dello stile di vita nella gestione della PCOS. I risultati sottolineano la necessità di piani di trattamento personalizzati che affrontino sintomi individuali e fattori dello stile di vita. Le future ricerche dovrebbero concentrarsi su studi longitudinali per comprendere meglio gli effetti a lungo termine di queste inteventi sulla gestione della PCOS. Gli operatori sanitari sono incoraggiati a considerare questi risultati nello sviluppo delle strategie di trattamento, poiché offrono indicazioni preziose per migliorare la qualità della vita delle donne con PCOS.

1. Introduction

1.1. Definition and Symptoms of PCOS

Polycystic ovary syndrome (PCOS) is considered as the most common endocrine and metabolic disorder among women in their reproductive ages, with an estimated prevalence range from 5 to 15% of the population (Morley LC et al., 2017).
PCOS is clinically characterised by various range of symptoms include polycystic ovaries, reproductive dysfunction (like infertility and pregnancy complications), unbalanced metabolic functions (like insulin resistance and diabetes type 2 and other), hyper-androgenism, menstrual dysfunction and the obesity (Escobar-Morreale HF, 2018)
The pathophysiology of PCOS is so complicated and in some extend still unclear. This disorder has a genetic heritability, and some affected genes are discovered so far. However, studies in this area shows that environmental factors are also associated. Most notable ones are diet and the increase of their body weight (Pasquali R et al., 2011)
PCOS is a heterogeneous condition, which means it has several root causes, as opposed to homogenous condition that have same root cause for all the patients. In PCOS first symptoms appears during the teenage years (Hecht Baldauff N and Arslanian S, 2014), although the symptoms are varied in severity in person to person and also can change during the time. Other symptoms that need to be mentioned are include acne, excess male pattern hair (hirsutism), male pattern alopecia and many other symptoms related to their reduction quality of life and consequently depression and anxiety are highly reported in patients that suffer from this disorder (Dokras A et al., 2011).

Regarding the diagnostic criteria of PCOS, a workshop convened in 2012 to resolve the ongoing debate concerning the most appropriate standards. However, the report resulting from this workshop was not published in a reputable scientific journal. This made its recommendations less influential. As a result, not everyone agrees on using the criteria proposed jointly by the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine in 2003, known as the Rotterdam criteria. So, there are still three different definitions for PCOS being used today (Héctor, F and Escobar-Morreale. 2018)

The Rotterdam definition stands as the predominant classification for PCOS, endorsed by many scientific societies and health authorities (Committee of the National Institutes of Health Evidence-Based Methodology Workshop on PCOS, 2012).

According to this definition, a diagnosis of PCOS can be made if a woman exhibits at least two of the following characteristics: clinical and/or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM) (Rotterdam sponsored-PCOS workshop group, 2004).

Each criterion used to define PCOS has its own clinical implications. Androgen excess can lead to visible signs like excess hair growth (hirsutism), acne, and hair loss (alopecia). Ovulatory dysfunction and irregular periods can cause infertility and increase the risk of uterine lining overgrowth (endometrial hyperplasia) or cancer. Isolated polycystic ovarian morphology (PCOM) poses a risk of ovarian hyperstimulation syndrome, mainly during fertility treatments. Generally, the more criteria a patient meets for PCOS, the more severe her condition tends to be (Jayaprakasan, K. et al. 2012)

As represented in Figure 1, next page, the most severe clinical presentation is the classic PCOS phenotype, characterized by both hyperandrogenism and irregular ovulation, regardless of the presence of polycystic ovarian morphology (PCOM).

The next most severe phenotype is ovulatory PCOS, which features hyperandrogenism and PCOM. The least severe phenotype is the non-hyperandrogenic phenotype, characterized by irregular ovulation and PCOM (Escobar-Morreale, H.F 2014).

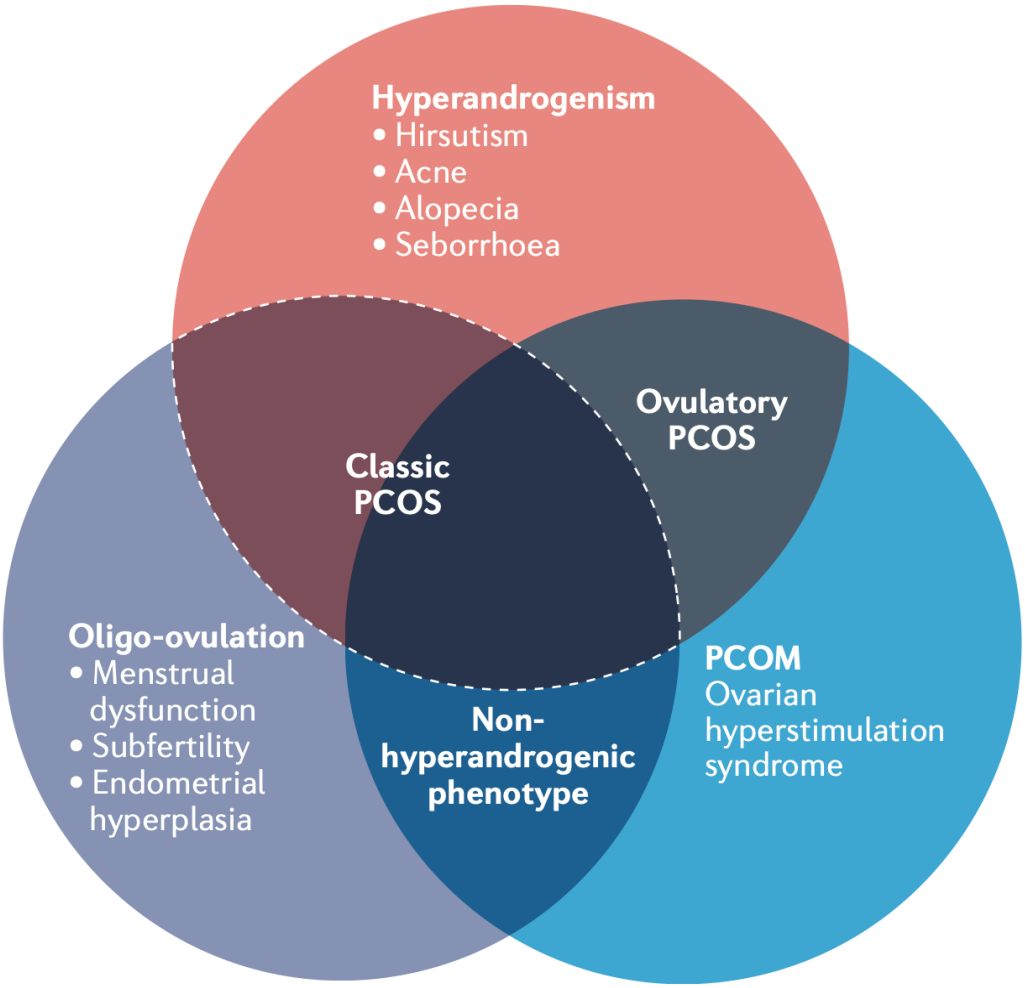


Figure 1: The varied characteristics of PCOS. (Héctor F. Escobar-Morreale. 2018)

1.2. History of Discovery

In 1935, Stein and Leventhal first described PCOS as a condition marked by symptoms like excess male hair growth in women (hirsutism), obesity and enlarged cystic ovaries (Stein. I and Leventhal. M, 1935).

However, it wasn't until 1990 that the World Health Organization (WHO) officially recognized it as (polycystic ovarian syndrome) in the international classification of diseases, 10^{th} revision (WHO, 1992).

Moreover, many drugs employed to manage the PCOS symptoms, such as oral contraceptive pills, anti-androgens, insulin sensitizers, or aromatase inhibitors, are utilized off-label. This is because neither the Food and Drug Administration (FDA) nor the European Medicines Agency has proved any drug directly for treatment of PCOS (Radosh, L. 2009)

The pharmaceutical industry hasn't shown much interest in PCOS, as seen in the number of clinical trials registered. By August 2017, there were only 28 studies on PCOS, while there were 4,632 on diabetes, even though both disorders are similarly prevalent worldwide (Soriguer, F. et al, 2012). This lack of interest makes PCOS the most common but overlooked disorder among women and poorly understood by patients, doctors, and scientists. Misunderstanding the syndrome and its long-term effects has led to limited research and development resources being allocated to it (Padmanabhan, V. 2009).

Additionally, the early research predominantly focused on the reproductive aspects of PCOS, often neglecting the metabolic and psychological components. It wasn't until the late 20th and early 21st centuries that a more comprehensive understanding began to emerge, recognizing PCOS as a complex endocrine disorder with wide-ranging impacts on women's health. This shift in perspective has spurred more holistic approaches to diagnosis and treatment, though significant gaps in knowledge and therapeutic options remain.

1.3. Causes of Polycystic Ovary Syndrome

PCOS is a complex condition influenced by various factors. Genetic predisposition, environmental factors, unhealthy lifestyle choices, diet patterns and potential exposure to infectious agents all contribute to the risk of developing PCOS. Additionally, conditions such as thyroid dysfunction, hyperprolactinemia, androgen-secreting tumors, Cushing

syndrome (characterized by excess cortisol levels), and hyperplasia further elevate the risk of developing PCOS (Goodarzi Mea. 2011).

Insulin resistance (characterized by elevated level of insulin) disturbs ovarian function, leading to increased androgen levels and subsequently anovulation (Diamanti-Kandarakis EKH. 2006). Moreover, PCOS affects the balance of gonadotropin-releasing hormone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (Marx TLMA. 2003). In addition to genetic factors play a significant role in the etiology of PCOS, involving candidate gene and single nucleotide polymorphisms (SNPs). Databases indicate that PCOS etiology involves 241 gene variations (Joseph SBR et al., 2015).

PCOS is largely influenced by genes responsible for key receptors like androgen receptor, Luteinizing Hormone (LH) receptors, Follicular Stimulating Hormone (FSH) receptors, and Leptin receptors (Xita N. 2002). When these genes have defects, they disrupt the body's biochemical pathways, leading to ovarian dysfunction. Various genetic variations, such as FSHR, FTO, VDR, IRS, and GnRHR polymorphisms, contribute to PCOS (Fang Shu-ying. 2018). As insulin and androgen levels increase, PCOS tends to worsen. High insulin levels, known as hyperinsulinemia, affect ovarian theca cells, leading to increased androgen levels (NuzhatShaikh R and Mukherjee Srabani. 2014).

Chemical exposure is another important factor like pesticide, vehicle and industrial pollutants, cleaning agents etc. Other products such as cosmetics, perfume, sunscreen, deodorant, hair dye and more are also implicated to increasing the rate of PCOS. Unfortunately, most consumers are completely unaware of this. These chemical stuffs are containing phthalates, parabens, isopropanol, glutaraldehyde, benzophenones and metals like nickel sulfate, cobalt chloride and more (O. Yang et al., 2015)

Chemical components like bisphenol A (BPA), commonly found in packaged and canned food over extended periods can contribute to serious problems like PCOS (A. konieczna et al., 2015).

1.4. Genetic Predisposition

PCOS shows a strong genetic association, with genes such as CAPN10, cytochrome P450 family, insulin gene, AR, FTO and FSHR being implicated.

Below there is a table display the cytogenetic locations and anomalies found in genes responsible for PCOS:

Gene	Cytogenic Location	Anomalies	Reference
CAPN10	2q37.3	Polymorphism	Margrit 2018
AR	Xq12	X inactivation	Urbanek 2017
FTO	16q12.2	Polymorphism mutations	Rizwan S 2018
Insulin gene	11p15.5	Polymorphism	Nida Ajmal 2019
P450 Family	various	Mutations, deletion polymorphism	NCBI 2018
FSHR	2p16.3	Gene variation	Aesha SH 2018

Table 1. Cytogenic location and anomalies found in genes responsible for PCOS.

According to the Table 1 the location of responsible genes and their anomalies are obvious.

1.5. Environmental Factors

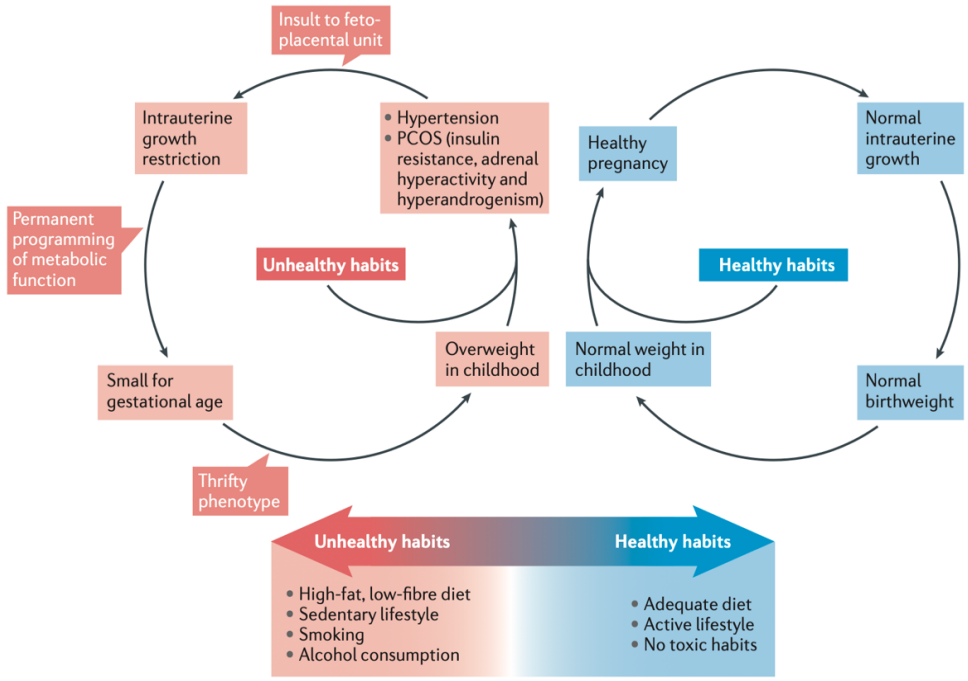


Figure 2. Environmental factors that impact PCOS

Environmental factors play a significant role in influencing non-genetic inheritance, such as inter uterine growth retardation and insulin resistance. During pregnancy, insults can lead to growth retardation in the womb, resulting in babies born small for gestational age. This can lead to a thrifty phenotype, characterized by insulin resistance, which may contribute to overweight issues in childhood.

Later in life, these individuals may develop conditions like hypertension, glucose intolerance, and polycystic ovary syndrome (PCOS), especially if exposed to risk factors like a sedentary lifestyle, unhealthy diet, smoking, and excessive alcohol consumption. These habits often cluster in families, as they are influenced by parental behaviour. However, switching to healthier lifestyle choices, such as a balanced diet, regular exercise, and avoiding harmful habits, may potentially prevent the inheritance of these traits (Oxford university press, 2005)

1.6. Diagnosis

Early detection can decrease the progression of Polycystic Ovary Syndrome (PCOS). Gynaecologists can diagnose PCOS from patient symptom descriptions, such as a history of oligomenorrhea, and morphological indicators like hirsutism. However, PCOS diagnosis relies on predefined criteria. In 1990, a National Institutes of Health (NIH) conference established the original diagnostic criteria for PCOS (A. Zawadzki, J.K. Dunaif, 1992).

Various parameters including anthropometric (blood pressure, cycle duration), ultrasound (follicle count, mean ovarian volume), endocrine (SHBG, testosterone, free androgen index (FAI), FSH, AMH, thyroid function tests), and lipid profiles can indicate PCOS. Glucose tolerance tests (GTT) and prolactin tests can also provide insights into PCOS conditions. Normal prolactin levels are typically below 500 mIU/L for women. Ultrasound imaging techniques, including transabdominal and vaginal ultrasound, can detect PCOS and visualize cysts (Seema Patel, 2018)

The Rotterdam criteria, established in 2003 by the Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), are the primary diagnostic guidelines for Polycystic Ovary Syndrome (PCOS).

These criteria define PCOS based on the presence of at least two out of three features:

1. Oligo-ovulation or anovulation (irregular or absent menstrual periods)
2. Clinical or biochemical signs of hyperandrogenism (excess male hormones), such as hirsutism (excessive hair growth), acne, or elevated levels of androgens in blood tests
3. Polycystic ovaries observed on ultrasound (the presence of multiple small follicles on the ovaries)

According to the Rotterdam criteria, a diagnosis of PCOS requires the exclusion of other conditions that may mimic its symptoms. These criteria expanded the diagnostic criteria for PCOS beyond the original NIH criteria from 1990, which required the presence of both hyperandrogenism and oligo-ovulation/anovulation for diagnosis.

The Rotterdam criteria allow for the diagnosis of PCOS in women who may only have one symptom, such as hyperandrogenism and polycystic ovaries, without necessarily having menstrual irregularities.

These criteria categorize PCOS into four phenotypes based on combinations of hyperandrogenism (HA), oligo-ovulation, and polycystic ovary morphology (PCOM) observed on ultrasound. Phenotypes A and B represent the classic PCOS, while phenotype C is termed "ovulatory PCOS," and phenotype D is considered "non-hyperandrogenic PCOS."

Approximately two-thirds of PCOS cases fall under phenotypes A and B, characterized by greater menstrual dysfunction, insulin resistance (IR), increased risk of metabolic syndrome, obesity, and atherogenic dyslipidemia.

1.7. Obesity

Obesity, a key component of metabolic syndrome, significantly impacts female fertility, primarily by altering the hypothalamic-pituitary-ovarian (HPO) axis. Obesity is often associated with higher circulating insulin levels, leading to increased ovarian androgen production. Excess adipose tissue then aromatizes these androgens to estrogen, resulting in negative feedback on the HPO axis and affecting gonadotropin production. These hormonal changes cause ovulatory dysfunction and menstrual abnormalities (Rachoń D, Teede H. 2010).

Weight gain is a prominent feature of PCOS. Community-based studies and meta-analyses indicate that women with PCOS have a threefold higher risk of obesity compared to those without the condition (Jungheim ES, Moley KH. 2010).

Data from an Australian longitudinal study suggest that each one-unit increase in BMI raises the risk of developing PCOS by nearly 10%, implying that the incidence of PCOS is likely to rise alongside global obesity rates.

Several factors contribute to weight gain in women with PCOS, including ethnicity. Caucasian women with PCOS are at a higher risk of obesity than their Asian counterparts, while childhood obesity predisposes white women, but not black women, to a PCOS diagnosis. Additionally, more clinically severe PCOS phenotypes (types A and B) are associated with higher obesity rates compared to less severe phenotypes (types C and D) (Moran C, et al. 2012).

Hyperinsulinemia is fundamental to the pathogenesis of PCOS, which is characterized by oligomenorrhea and hyperandrogenism. The presence of obesity exacerbates insulin resistance and intensifies the symptoms of PCOS (Moran LJ, et al. 2015).

Increased androgen production in PCOS leads to the deposition of visceral fat, which further enhances insulin resistance and hyperinsulinemia, perpetuating this vicious cycle (Broughton DE, Moley KH. 2017).

Obesity is a common characteristic of PCOS. A meta-analysis of cross-sectional and retrospective studies demonstrated a higher prevalence of obesity (BMI > 30 kg/m²) in individuals with PCOS compared to healthy women, with a relative risk of 2.77 (95% CI 1.88, 4.10; PCOS n=4165; controls n=4885). The reported prevalence of obesity in

women with PCOS varies, likely due to geographical, environmental, and population differences (Lim SS, et al. 2012).

There is uncertainty about whether PCOS leads to weight gain and obesity or if obesity contributes to the development of PCOS. Additionally, understanding the role of adiposity in PCOS requires more comprehensive measurements than BMI (Teede HJ, et al. 2013).

1.8. Meta Analysis

A meta-analysis revealed that overweight or obese women with PCOS experience significantly worse metabolic and reproductive outcomes compared to healthy-weight women with PCOS (Lim SS, et al. 2013).

Palomba and his colleagues confirmed that obesity has a bidirectional relationship with PCOS, noting that excessive weight gain can unmask a latent PCOS condition. Insulin resistance (IR) promotes the development of visceral adiposity in women with PCOS, though the role of androgens is less clear (Spritzer PM, et al. 2015).

Tosi and his team recently demonstrated a correlation between adiposity, IR, and free testosterone levels in women with PCOS (fat mass measured by dual-energy X-ray absorptiometry (DXA), IR assessed with a euglycemic clamp, and serum free testosterone measured by liquid chromatography–MS, n=100 women with PCOS.

However, insulin sensitivity, rather than adiposity, was found to be an independent predictor of free testosterone concentrations. The central-to-peripheral fat ratio identified by DXA was related to androgen levels in twenty-four women with PCOS. The complex relationship between androgens and obesity is gradually being understood; adipocytes appear prone to hypertrophy when exposed to excess androgens, and both adipose tissue hypertrophy and hyperandrogenism are linked to IR. It is known that even a modest weight reduction of 5% can improve PCOS symptoms in overweight or obese women with PCOS (Moran LJ, et al. 2009).

It remains debated whether women with PCOS have increased abdominal adiposity compared to women in the general population. Since there is no standardized diagnostic method for abdominal obesity, various methods are employed.

The Visceral Adiposity Index (VAI), a simple surrogate marker of visceral adiposity using BMI, waist circumference, TAG, and HDL measurements, has been increasingly utilized since its introduction in 2010 (Amato MC, et al. 2010).

Anthropometric studies including waist circumference measurements have shown that women with PCOS typically have increased abdominal fat distribution, regardless of BMI. A meta-analysis by Lim et al. also reported a higher prevalence of central obesity in women with PCOS (risk ratio 1.73; 95% CI 1.31, 2.30; PCOS n=1191; controls n=2396) (figure 3) (Herriot A, et al. 2008).

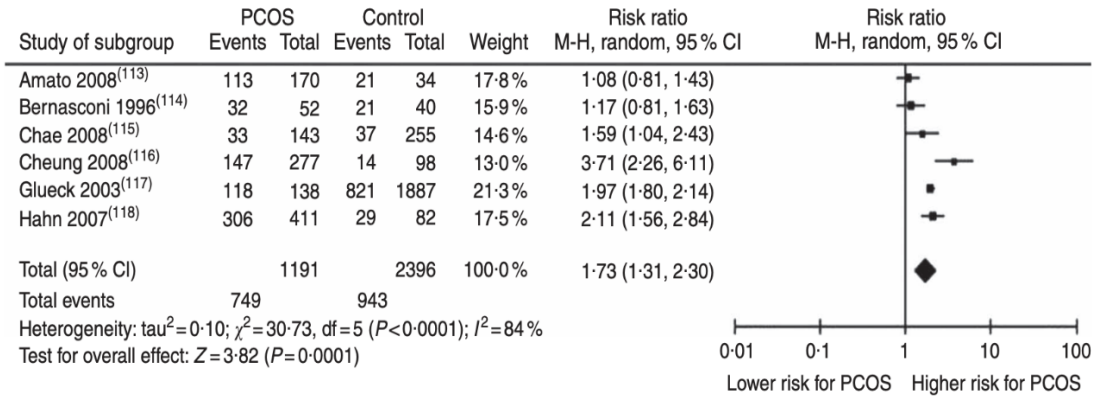


Figure 3: a meta-analysis comparing the risk of central obesity in women with PCOS versus controls (Lim SS, et al. 2012)

Key Elements:

These studies include the analysis includes data from six studies: Amato 2008, Bernasconi 1996, Chae 2008, Cheung 2008, Glueck 2003, and Hahn 2007.

Each study lists the number of events (cases of central obesity) and the total number of participants for both PCOS and control groups.

The risk ratio (RR) for each study is shown with 95% confidence intervals (CIs). These ratios indicate the likelihood of central obesity in women with PCOS compared to controls.

Overall Findings:

The combined RR for all studies is 1.73 (95% CI: 1.31, 2.30), indicating that women with PCOS are significantly more likely to have central obesity compared to controls.

The diamond at the bottom of the plot represents the overall effect size, showing that the combined risk ratio is significantly greater than 1, indicating higher central obesity risk in women with PCOS.

Interpretation:

The meta-analysis shows a consistent trend across multiple studies that women with PCOS have a significantly higher risk of central obesity compared to women in the general population. The substantial heterogeneity indicates that while the trend is consistent, the magnitude of the risk varies across different studies. This suggests that factors such as study design, population characteristics, and measurement methods might influence the results.

As a recap, intrinsic and extrinsic factors, including genetics, hormonal influences, and lifestyle, contribute to obesity in PCOS. Obesity-related genes like FTO (fat mass and obesity-associated gene) and MC4R (melanocortin-4-receptor gene) are linked to PCOS and may have a stronger impact on women with PCOS compared to those without.
Hormonal factors such as insulin resistance (IR) and hyperandrogenism (HA) further contribute to the development and severity of PCOS. However, the interactions between obesity, IR, and HA are complex and challenging because they often occur together. Additionally, higher rates of anxiety, depression, and disordered eating behaviors (binge-eating), which are common in women with PCOS, also contribute to obesity (Dokras A, et al. 2018).
The interaction between obesity, insulin resistance (IR), and hyperandrogenism (HA) in PCOS is intricate and exacerbates both the prevalence and severity of the condition. As first identified by Dunaif et al., IR is a core feature of PCOS. Studies using euglycemic hyperinsulinemia clamps report that IR is present in 75% of lean women and 95% of overweight women with PCOS, indicating that obesity further exacerbates IR (Stepto NK, et al. 2013).

When obesity, particularly abdominal obesity, coincides with IR, it leads to HA, while HA independently promotes abdominal fat accumulation, which can further aggravate IR. Obesity often raises levels of cholesterol, triglycerides, free fatty acids (FFAs), and various apolipoproteins. The increase in FFAs contributes to IR by reducing glucose

uptake in muscle cells. FFAs may also induce IR by activating certain kinases and reducing tyrosine phosphorylation of IRS-1(Torre-Villalvazo I, et al. 2018).

The resulting compensatory hyperinsulinemia is thought to stimulate androgen production in the ovarian theca cells via the PI3K and MAPK signaling pathways, ultimately leading to HA. In the ovaries, hyperinsulinemia also affects follicular development by increasing insulin growth factor-1 content and inhibiting folliculogenesis. Additionally, hyperinsulinemia is believed to reduce hepatic production of sex hormone-binding globulin (SHBG), increasing the bioavailability of circulating androgens in PCOS (Tosi F, et al. 2011).

Excess weight worsens insulin resistance (IR) and aggravates hyperandrogenism (HA) in PCOS. HA is believed to promote central fat distribution, leading to a higher prevalence of central obesity in women with PCOS, independent of their BMI.

Central adiposity, a marker of visceral adipose tissue (VAT), is strongly associated with IR and other metabolic risks due to increased inflammation and oxidative stress. More research is needed to understand the interactions between IR and HA in relation to obesity, with a particular focus on the role of central adiposity, as VAT differentially regulates multiple adipokines (Tay CT, et al. 2019).

Given the complex relationship between obesity and PCOS, which is often influenced by psychological and environmental factors, lifestyle management should be the first line of treatment. This approach, as recommended by international evidence-based guidelines by Teede et al., should emphasize weight gain prevention, weight maintenance, and modest weight loss when necessary (Moran LJ, et al. 2009).

1.9. Risk of Infertility

Infertility is a common clinical feature of PCOS, affecting 70 to 80% of women with the condition. The WHO defines infertility as a disease of the reproductive system, characterized by the inability to achieve a clinical pregnancy after 12 months or more of regular, unprotected sexual intercourse (World Health Organization, 2020).

Globally, about 10% of women experience secondary infertility, and approximately 2% face primary infertility. Over the past 20 years, infertility rates have only slightly declined, with factors such as increased age and demographic region contributing to

higher rates. A retrospective study from the United Kingdom found that among 786 women with PCOS, 66% reported infertility and 17.5% had persistent involuntary infertility. In contrast, among 1,060 women without PCOS, 6% reported infertility and only 1.3% reported persistent involuntary infertility (Wild S, et al. 2000)

The relationship between obesity and reproductive functions in PCOS is well known, though the mechanisms leading to infertility are complex and multifaceted. Numerous studies have documented the positive linear relationship between increased BMI and the risk of a PCOS diagnosis, as well as the independent associations of these factors with infertility (Van der steeg JW, et al. 2008).

A key study by Joham et al. conducted a longitudinal analysis using data from the community-based Australian Longitudinal Study on Women's Health. This study reported that 72% of 309 women with PCOS experienced infertility, compared to 16% of 4,547 women without PCOS (Joham AE, et al. 2015).

The study also found that with each increase in BMI category, the use of fertility hormones was higher among women with PCOS; however, there was no significant interaction between PCOS, BMI, and infertility risk (Dunaif A & Graf M, 1989).

This finding is particularly interesting given the clear role obesity plays in PCOS and infertility. Obesity exacerbates insulin resistance (IR) and hyperandrogenism (HA) in PCOS. Since IR independently and synergistically contributes to PCOS alongside obesity, it can be proposed that IR is a primary driver of infertility in PCOS, independent of BMI (Steingold KA, et al. 1986).

Obesity is believed to contribute to infertility through insulin resistance (IR), a major factor causing anovulation in PCOS (Willis D, et al. 1996)

IR increases the frequency of gonadotropin-releasing hormone (GnRH) pulses by affecting the hypothalamus–pituitary–adrenal axis, which is thought to disrupt ovulation. Elevated insulin levels in anovulatory women with PCOS likely cause premature maturation of granulosa cells (Mascarenhas MN, et al. 2012)

This premature maturation can occur because granulosa cells respond to luteinizing hormone (LH) despite peripheral IR. This response has been observed only in anovulatory women with polycystic ovaries, not in ovulatory women. This suggests that granulosa cells in anovulatory PCOS women are at a more advanced developmental stage for their size, contributing to anovulation. Consequently, the maturation of small healthy follicles

is impaired, preventing ovulation and reducing fertility. Other mechanisms of anovulation in PCOS remain unclear (Kumar P & Sait SF, 2011).

1.10. Risk of Diabetes Mellitus

Women with PCOS face a two- to threefold higher risk of gestational diabetes mellitus (GDM) compared to those without PCOS. Normally, pregnancy involves physiological adaptations that lower insulin sensitivity in the second half to support fetal growth, making all pregnant women susceptible to GDM.

Women with PCOS, already experiencing insulin resistance (IR), are at even greater risk of developing GDM. Annually, GDM affects about 14% of pregnancies worldwide, involving approximately 18 million births.

However, GDM diagnostic criteria vary significantly across countries, and the cutoff values are controversial. Evidence-based guidelines recommend a 75-g oral glucose tolerance test (OGTT) before 20 weeks of pregnancy for early detection and management of GDM, aiming to prevent adverse pregnancy outcomes such as large-for-gestational-age babies and medicalized deliveries.

Several features of PCOS increase the risk of gestational diabetes mellitus (GDM) in affected women. Pre-pregnancy weight is a significant risk factor, with a higher BMI before pregnancy correlating with a greater risk of GDM, regardless of PCOS diagnosis. A case-control study of 1,146 women with singleton pregnancies found that a one-unit increase in pre-pregnancy BMI raised the odds of GDM by 7%, with PCOS not significantly contributing to this increase.

Excessive gestational weight gain (GWG) also elevates GDM risk. Only 30% of women meet the Institute of Medicine's GWG guidelines, while 47% experience excessive GWG. A meta-analysis of 42 studies indicated that women with PCOS had significantly higher GWG, gaining an additional 400 grams compared to women without PCOS, particularly in Asian and European populations. However, when comparing BMI-matched controls, PCOS was no longer associated with increased GWG, highlighting pre-pregnancy BMI as the main risk factor.

Excessive GWG during the first half of pregnancy raises the risk of abnormal OGTT results between weeks 22 to 29, leading to a higher likelihood of needing aggressive insulin therapy later in pregnancy. Women with PCOS, whether lean or overweight before pregnancy, gain more weight during pregnancy than their non-PCOS counterparts, with lean women gaining 1.9 kg and overweight women gaining 2.4 kg more

Women with pre-pregnancy overweight BMI and PCOS tend to gain more weight in the second and third trimesters compared to those without PCOS. This increased weight gain in the later stages of pregnancy is linked to various complications like larger babies, preeclampsia, more cesarean deliveries, and gestational diabetes.

However, there's no notable difference in weight gain throughout pregnancy when compared to women with pre-pregnancy obesity but without PCOS. This suggests that both pre-existing obesity and excessive weight gain during pregnancy contribute to complications in women with PCOS. Insulin resistance, influenced by both PCOS and pregnancy, along with psychological factors and maternal age, may predispose these women to gaining too much weight.

Pre-pregnancy BMI is a significant predictor of weight gain during pregnancy regardless of PCOS diagnosis. Understanding the impact of weight gain during pregnancy on the risk of gestational diabetes in subsequent pregnancies is crucial.

Studies indicate that a high percentage of women who had a normal BMI before pregnancy become overweight or obese within five years after giving birth. Women who are overweight or obese when they conceive have a significantly higher chance of retaining more than 5 kg of weight one year after giving birth. This increases the likelihood of entering subsequent pregnancies overweight or obese, which further raises the risk of excessive weight gain during pregnancy and gestational diabetes.

Factors like ethnicity and advanced maternal age also contribute to the risk of gestational diabetes. For instance, studies have shown that South Asian and Chinese women have a higher prevalence of gestational diabetes across all BMI levels compared to the general population.

This suggests that women with these ethnicities who also have PCOS may face an elevated risk of PCOS-related gestational diabetes. Additionally, advanced maternal age, due to delaying pregnancy, is associated with an increased risk of gestational diabetes. Women with PCOS who conceive later in life are thus at an even higher risk of developing gestational diabetes.

2. Lifestyle Modifications

In recent years, lifestyle modifications have become the cornerstone of interventions for managing PCOS. These modifications are considered the first-line treatment for patients dealing with overweight or obesity. The most effective interventions include dietary changes, increased physical activity, and exercise, along with strategies to ensure long-term adherence.

Lifestyle modifications also help regulate ovulation and the menstrual cycle, thereby increasing successful pregnancy rates in PCOS patients. Studies indicate that nearly half of PCOS patients experience improved menstrual regularity and ovulation with lifestyle changes. Additionally, these modifications can alleviate anxiety and enhance the quality of life, especially in obese women with PCOS.

According to the studies, a healthy diet combined with educational programs leads to greater weight loss. For instance, Oberg E found that even minimal behavioral intervention can help people lose weight. The outcomes differ significantly between diet modifications, exercise modifications, and their combination. A high-protein diet results in more weight loss compared to a standard protein diet. However, there is no significant difference between the effects of a vegan diet and a calorie-restricted diet, nor between a low-GI diet and a hypocaloric healthy eating diet.

Lifestyle modifications including diet, exercise, and sleep, play crucial roles in managing PCOS by regulating insulin sensitivity, maintaining a healthy weight, and normalizing androgen production.

These changes have been shown to help restore ovulation and regular menstrual cycles, thereby increasing pregnancy rates in overweight or obese anovulatory women with PCOS.

Obesity is a key factor in the development of PCOS; it decreases the levels of sex-hormone-binding globulin in females, leading to elevated androgen levels, which disrupt normal ovulatory function. Additionally, obesity is linked to higher risks of metabolic syndrome, type 2 diabetes, and insulin resistance.

Studies comparing the effects of lifestyle modifications alone versus in combination with metformin have found that lifestyle changes can reduce insulin resistance and increase serum levels of sex-hormone-binding globulins more effectively than metformin alone. Further research has analyzed the impacts of lifestyle modifications combined with other

interventions, demonstrating improvements in PCOS symptoms. For example, Negar's analysis of 12 randomized controlled trials involving 608 participants found a significant reduction in subcutaneous fat in those following a lifestyle regimen (including daily physical activity and limited food intake) combined with metformin, compared to those combining lifestyle changes with a placebo. Additionally, both lifestyle modifications alone and in combination with hormonal contraceptives have been shown to improve sexual function.

Lifestyle component	General recommendations
Alcohol consumption	• Alcohol cessation is best[127]
Cigarette smoking	• Complete cessation is best • Reduce exposure to passive smoking
Toxin exposure	• Reduce exposure to toxins and other hazardous chemicals
Intercourse frequency	• Every 2–3 d to optimize chance of pregnancy
Complementary therapies	• Effectiveness is yet to be properly evaluated and still unknown
Psychological stress	• Reduce triggers or sources of stress whenever possible to improve libido, couple relationship, and intimacy
Physical activity	• ≥150 min/wk moderate or 75 min/wk vigorous intensity for prevention of weight gain and general health[128] • ≥250 min/wk moderate or 150 min/wk vigorous intensity for modest weight loss and prevention of weight regain[128] • Minimize sedentary time[128] • Strength training exercises on 2 nonconsecutive days[128]
Nutrition	• No specific dietary pattern recommended • Dietary approach should be balanced and tailored to the individual lifestyle, preferences, and medical needs for optimal implementation • Inconsistent evidence relating to caffeine intake from tea, coffee, and sugared beverages currently available • Folate supplementation of 0.4 mg/d. Women with a BMI ≥30 kg/m^2, who have previously given birth to an infant with neural tube defects, women who are receiving antiepileptic medication, or who have diabetes should be supplemented with 5 mg/d

Table 2: Lifestyle Recommendations to Improve Fertility in Women of Reproductive Age

The above table 2 provides a comprehensive guide for lifestyle modifications aimed at managing PCOS. Key areas of focus include cessation of harmful habits like smoking and alcohol consumption, reducing stress, maintaining regular physical activity, and adopting a balanced diet. These modifications are vital for improving overall health and mitigating PCOS symptoms.

2.1. Weight Management

The clinical complexity and variability of PCOS highlight the unclear relationship between obesity and the syndrome. However, it is well-established that obesity exacerbates insulin resistance and hyperandrogenism. Research indicates that even a modest weight loss of 5–10% can significantly improve reproductive issues, metabolic

dysfunction, and psychological symptoms in PCOS patients. Therefore, weight management is recommended as an initial step for overweight or obese individuals with PCOS (Panidis D, et al. 2013).

For PCOS patients troubled by infertility, it is advised that those with obesity first focus on weight loss before pursuing infertility treatments, as obesity is associated with higher risks of miscarriage and preeclampsia in pregnant women with PCOS. Overweight and obese PCOS patients are also more prone to mood disorders such as anxiety and depression, though the extent of this increased risk and its impact on the syndrome's severity remains unclear. For patients unable to lose weight through diet and exercise alone, anti-obesity medications like orlistat may be considered (Saleem F and Risvi SW, 2017).

Even women with PCOS who maintain a normal weight and BMI face increased risks for metabolic disorders and chronic fatigue. These patients are also encouraged to follow diet and exercise programs to improve insulin sensitivity. More research is needed on the effects of weight management in normal-weight PCOS patients.

Overall, it is recommended that women with PCOS monitor their weight, prevent excessive weight gain, and maintain a healthy BMI and waist circumference (Akbarzade S, et al. 2012).

In this section, Table 3 presents a set of lifestyle recommendations specifically designed for weight management in women with PCOS aged 18 years and older. These recommendations encompass dietary modifications, physical activity guidelines, and behavioral strategies aimed at promoting effective weight loss and improving overall health outcomes. The guidelines are tailored to address the unique challenges faced by women with PCOS, emphasizing sustainable lifestyle changes that can help mitigate the symptoms and complications associated with the condition.

	Recommendation
Daily energy intake	• Weight loss: 1,200–1,500 kcal/d *or* a deficit of 30% from total daily energy intake to promote 5–10% loss of initial weight within 6 mo[a,b] • Weight gain prevention: dependent on weight, age, other comorbidities, and physical activity. Monitor required intake based on changes in weight and quality of body function
Physical activity	• Weight gain prevention: ≥150 min/wk moderate or 75 min/wk vigorous activity, minimizing sedentary time and including muscle-strengthening activity on 2 nonconsecutive d/wk) • Modest weight loss[b]: ≥250 min/wk moderate or 150 min/wk vigorous activity
Diet type	Weight loss[b] and weight gain prevention: • A variety of balanced dietary approaches consistent with general population recommendations • Sustainable and relevant to personal lifestyle
Professional guidance	Weight loss[b] and weight gain prevention: • Referred to suitably trained health professionals (general practitioners, dietitians, exercise physiologists, psychologists, fertility specialists, endocrinologists, obstetricians, and gynecologists) where comorbidities arise
Behavioral strategies	Weight loss[b] and weight gain prevention: • Goal setting using SMART approach • Self-monitoring • Stimulus control • Problem solving • Assertiveness training • Slower eating • Reinforcing changes • Relapse prevention

Table 3: Lifestyle Recommendations for Weight Management in Women with PCOS Aged 18 and Older (Stephanie P, et al. 2021)

Table 3 outlines comprehensive lifestyle recommendations for weight management in women with PCOS aged 18 years and older. The recommendations cover several key areas including daily energy intake, physical activity, diet type, professional guidance, and behavioral strategies. For daily energy intake, it is suggested that weight loss can be achieved by consuming 1,200–1,500 kcal/day or creating a caloric deficit of 30% to promote a 5–10% reduction in initial weight within six months. For weight gain prevention, the intake should be adjusted based on individual factors like weight, age, comorbidities, and physical activity levels, with regular monitoring to ensure the necessary intake changes.

In terms of physical activity, to prevent weight gain, at least 150 minutes per week of moderate or 75 minutes per week of vigorous activity is recommended, along with muscle-strengthening activities on two non-consecutive days per week. For modest weight loss, increasing this to 250 minutes per week of moderate or 150 minutes per week of vigorous activity is suggested. The diet type recommendation emphasizes a balanced dietary approach that aligns with general population guidelines and is sustainable and tailored to personal lifestyles.

Professional guidance is essential for both weight loss and weight gain prevention, recommending referrals to trained health professionals, including general practitioners,

dietitians, exercise physiologists, psychologists, fertility specialists, endocrinologists, obstetricians, and gynecologists, especially when comorbidities are present. Behavioral strategies include goal setting using the SMART approach, self-monitoring, stimulus control, problem-solving, assertiveness training, slower eating, reinforcing changes, and relapse prevention. These comprehensive strategies are designed to support effective and sustainable weight management for women with PCOS.

Table 4 summarizes common pharmacologic approaches to reducing obesity in women with PCOS. The effectiveness of weight loss is rated on a scale from 1 (least effective) to 10 (most effective), which ranks liraglutide, orlistat, and metformin in descending order of effectiveness. Phentermine and sibutramine are FDA-approved drugs for obesity in general populations, with sibutramine shown to enhance weight loss in PCOS patients when combined with lifestyle modifications beyond what is achieved with diet and placebo alone.

Metformin

• Mode of action: decreases hepatic glucose production, decreases intestinal absorption of glucose, improves insulin sensitivity by increasing peripheral glucose uptake and utilization
• Dose: 1.5–2.55 g/day, 1–2 g/day if XR, in divided doses with meals. Dose-response present, start with lowest dose
• Use in pregnancy: Increases live births, not teratogenic, reduces gestational diabetes
• Contraindications: creatinine clearance b40 mL/min
• Use with caution: creatinine clearance b60 mL/min moderate–severe heart failure, acute myocardial infarction, before major surgery • Rare side effects: intractable nausea, gastritis, vomiting
• Common side effects: nausea, vomiting, diarrhea
• Weight loss effectiveness: 5, (8 when combined with Liraglutide)

Liraglutide

• Mode of action: long-acting glucagon-like peptide-1 receptor agonist, binding to the same receptors as does endogenous GLP-1, stimulates insulin secretion, central appetite suppression.
• Dose: 1.2–1.8 μg/once/day subcutaneously, dose response present. 3 mg/ once per day (Saxenda). Start with lowest dose.
• Use in pregnancy: not recommended
• Contraindications: History of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, acute or chromic pancreatitis, gastroparesis. • Use with caution: previous pancreatitis
• Rare side effects: intractable recurrent nausea, vomiting
• Common side effects: nausea, vomiting, headache
• Weight loss effectiveness: 7, (8 when combined with Metformin)

Thiazolidinediones

• Mode of action: PPAR-gamma agonists, reduce insulin resistance
• Dose: Pioglitazone (45 mg, up to 15 mg, three times/day with meals); Rosiglitazone (4–8 mg/day, divided doses with meals). Start with lowest dose. • Use in pregnancy: not recommended
• Contraindications: congestive heart failure, peripheral edema

• Use with caution: safety during pregnancy not well understood
• Rare side effects: bladder cancer, bone fracture in women
• Common side effects: peripheral edema
• Weight loss effectiveness: 0–1, weight gain possible

Orlistat
• Mode of action: Reduces fat absorption. Inhibits gastric and pancreatic lipases, blocks hydrolysis of dietary triglycerides to absorbable fatty acids, triglycerides excreted unchanged. • Dose: 120 mg up to 3 times/day with meals, restrict dietary fat to b30% of calories, add fat-soluble vitamin daily
• Use in pregnancy: contraindicated (fat soluble vitamin malabsorption)
• Contraindications: acute or chronic cholecystitis, obstructive bowel disease.
• Use with caution: pancreatic or liver disease
• Rare side effects: Oxaluria, kidney stones
• Common side effects: flatulence, steatorrhea, diarrhea, increased stool frequency.
• Weight loss effectiveness: 5

Acarbose
• Mode of action: Delayed glucose absorption with lowering of postprandial hyperglycemia, competitive-reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolase enzymes.
• Dose: 50 mg every 8 h if b60 kg; 100 mg every 8 h if N60 kg, take with first bite of meal
• Use in pregnancy: not recommended
• Contraindications: Reduced renal function (eGFR b25 mL/min/1.73 m^2). Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, predisposition to intestinal

obstruction.
• Use with caution: eGFR b50 mL/min/1.73 m^2, previous small or large bowel partial resection
• Common side effects: Abdominal pain, diarrhea, flatulence
• Weight loss effectiveness: 5

Table 4: Pharmacologic approaches to weight loss in polycystic ovary syndrome (Charles Je at al. 2019)

2.2. Physical Activity

As research increasingly focuses on the roles of physical activity in human health, evidence has shown that exercise benefits women with PCOS, a view that is gaining acceptance among both doctors and patients. Determining the appropriate exercise intensity and frequency to alleviate PCOS symptoms can be challenging. A recent study reported that improvements in health outcomes are more closely linked to exercise intensity rather than exercise alone (Otto-Buczkowska E, et al. 2018)

One randomized controlled trial (RCT) indicated that vigorous exercise (eight consecutive weeks with three supervised sessions per week during the final four weeks) had a significant impact on PCOS outcomes, particularly in reducing insulin resistance. Each session, lasting approximately 60 minutes, included 40 minutes of individualized

exercise on a cycle ergometer or motorized treadmill, preceded by a 10-minute warm-up and followed by a 10-minute cool-down (Woodward A, et al. 2020)

However, many women with PCOS tend to be more sedentary and less likely to engage in vigorous exercises. Moderate aerobic exercise has also been shown to improve insulin sensitivity in the short term. Additionally, other studies suggest that vigorous aerobic exercise and resistance training can improve insulin sensitivity and reduce abnormal androgen levels in women with PCOS. It is recommended that women with PCOS engage in at least 150 minutes of aerobic activity per week, including more than 90 minutes of intensive exercise (Stephano NK, et al. 2020)

2.3. Mood and Sleep Modifications

Increasing evidence indicates that both adolescent and adult females with PCOS experience significant mood disturbances, including depression and anxiety. Studies have shown that women with PCOS are at a higher risk for depression, anxiety, and perceived stress compared to those without the condition.

Given this association, screening and effective interventions for mood disorders in women with PCOS are recommended (Simon S, et al. 2020).

The link between depression and PCOS can be attributed to common factors such as excessive androgen secretion, insulin resistance, and obesity. These shared connections may aid in developing potential therapies for managing depression in women with PCOS. Appropriate mood modification strategies can significantly improve the quality of life for these women.

Additionally, sleep disorders are prevalent among women with PCOS and are considered both a risk factor and a contributing factor to the condition. Effective management of sleep issues is crucial as sleep deprivation is associated with increased risks of insulin resistance, obesity, and type 2 diabetes (Chen X, et al. 2020)

Mechanisms linking sleep deprivation to PCOS involve autonomic pathways, endocrine disorders, and inflammatory status, which are critical in PCOS development.

Studies have demonstrated that women who sleep less than 5 hours per night have a higher risk of developing type 2 diabetes compared to those who sleep 7 to 8 hours.

Moreover, sleep quality, measured through the percentage of rapid eye movement sleep, is generally lower in obese females with PCOS than in normal-weight or obese females

without PCOS. Ensuring adequate and high-quality sleep can reduce risks associated with obesity, insulin resistance, and cardiovascular issues, making sleep modification an essential component of PCOS management (Tasali E, et al. 2006)

3. Food Pattern and Type of Diets

While reducing calorie intake and inducing weight loss are recommended for women with PCOS who have obesity, most current dietary recommendations are based on studies involving obese women without PCOS.

Evidence suggests that no specific diet type is superior to others. However, some studies have shown that a low-carbohydrate diet, where carbohydrates constitute less than 45% of daily calories, may help decrease body mass index (BMI) and serum total cholesterol levels in women with PCOS. Furthermore, maintaining a low-carbohydrate diet for over a month can significantly increase levels of follicle-stimulating hormone and sex-hormone-binding globulin.

Despite some evidence supporting the benefits of a low-carbohydrate diet for PCOS, the exact mechanisms remain unclear. It is well known that metformin can similarly reduce body weight. Some studies have compared the effects of dietary modifications alone to a combination of metformin and lifestyle changes for managing PCOS. These studies indicate that dietary changes alone can reduce insulin resistance and increase serum levels of sex-hormone-binding globulin more effectively than metformin.

Importantly, weight loss can improve PCOS features regardless of dietary composition. However, lifestyle modifications, including diet changes, often fail to produce long-term results, like the outcomes seen with anti-obesity drugs. This lack of long-term success may be due to the tendency for women to regain weight and struggle to maintain a normal BMI over time.

Figure 4 provides a comprehensive overview of dietary recommendations aimed at reducing the features of Polycystic Ovary Syndrome (PCOS). It highlights various dietary components and their effects on PCOS symptoms. Key recommendations include increasing the intake of plant foods rich in alpha-linolenic acid, vitamins (such as D-vitamin, B12, and folate), fibbers, polyphenols, and inositol. These nutrients are essential for improving metabolic and reproductive health in women with PCOS.

Conversely, the image advises against fat diets and high carbohydrate intake. Instead, it suggests consuming complex carbohydrates, which have a lower impact on insulin levels.

It also emphasizes the importance of avoiding deficiencies in essential minerals like zinc, magnesium, selenium, and chromium. Animal-based foods rich in omega-3 fatty acids, such as EPA and DHA, are recommended, while those high in saturated fats should be minimized. This balanced approach to diet can help manage and alleviate PCOS symptoms effectively.

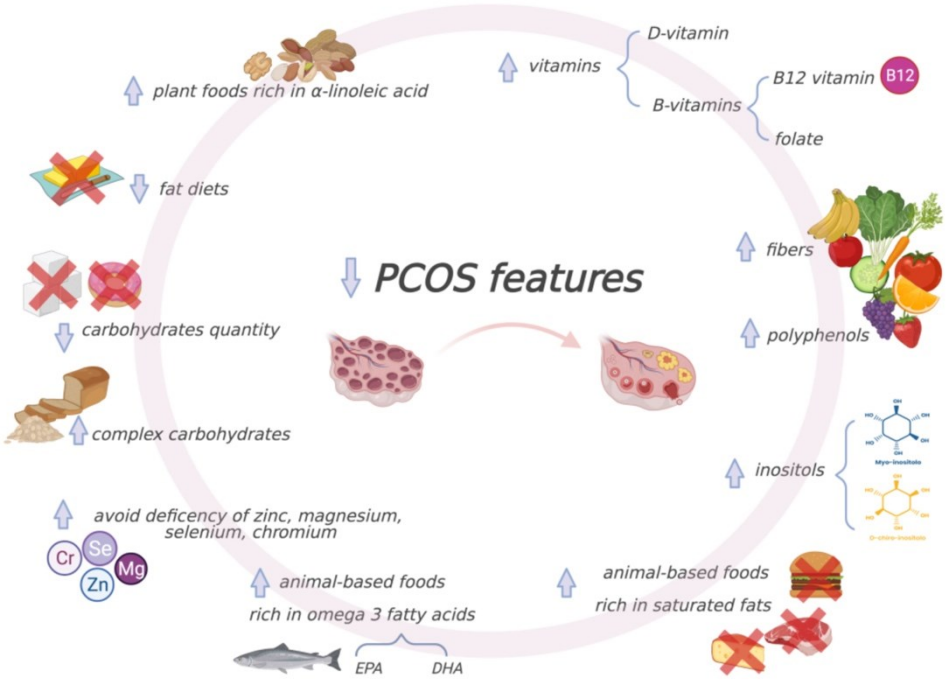


Figure 4: Macro and micronutrients beneficial for polycystic ovary syndrome. Created with BioRender.com (2021). EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; ↑high; ↓low.

By following these dietary guidelines, the features of PCOS, such as insulin resistance, inflammation, and hormonal imbalances, can be mitigated. The illustration indicates that improving diet quality with these specific nutrient focuses can lead to healthier ovarian function and reduce PCOS symptoms.

Losing excess weight can significantly improve PCOS symptoms and reduce the risk of long-term health problems. Diet composition is also crucial, and dietary modifications are recommended to enhance metabolic status.

However, women with PCOS often struggle with long-term adherence to dietary recommendations, leading to minimal improvements in metabolic and reproductive

outcomes. Additionally, they tend to underreport their dietary intake, making effective nutritional counselling challenging.

Recommendations for women with PCOS emphasize the benefits of low-fat diets and the drawbacks of high-carbohydrate diets. Suggested dietary changes include balancing energy intake, limiting saturated and trans fats, increasing unsaturated fats, boosting fruit and vegetable intake, and reducing simple sugars and salt. These recommendations align with the concept of a "healthy diet" and are inherent to regional diets like the Mediterranean diet (MD).

The MD, characterized by high consumption of extra virgin olive oil, nuts, and legumes, and low intake of animal and processed foods, has been associated with reduced diabetes risk and improved insulin resistance (IR) in overweight PCOS patients.

Adherence to the MD is linked to reduced inflammation and down-regulation of disease-related immunological pathways, as well as being rich in antioxidants that reduce oxidative stress. Including regular physical activity, the MD has been shown to significantly improve IR and other health measures.

Low glycemic index/glycemic load (GL) diets, which manage the total intake of dietary carbohydrates and their quality, are also beneficial in improving IR and other health outcomes in women with PCOS. Research supports the effectiveness of low-carbohydrate diets in treating infertility and improving metabolic markers. Recent studies highlight that a low-carbohydrate ketogenic diet (LCKD) can effectively promote weight loss and improve insulin resistance in women with PCOS.

3.1. Ketogenic Diet

Ketogenic diets involve reducing carbohydrate intake to usually less than 50 grams per day while increasing the proportions of proteins and fats. In a low-carbohydrate ketogenic diet (LCKD), 75% of daily energy comes from fats, 20% from protein, and 5% from carbohydrates. Although not high in protein, the LCKD is typically high in fats, adequate in protein, and low in carbohydrates. This diet is considered safe for short cycles in women with PCOS, with no evidence of long-term side effects. The LCKD helps preserve lean body mass due to adequate dietary protein intake. Women with PCOS have experienced reductions in body weight, blood glucose, and insulin levels after 12 weeks on the diet, correcting hyperinsulinemia and HOMA-IR, thereby improving body

composition. After six months, women with PCOS and obesity showed significant improvements in fasting insulin, leading to an enhanced LH/FSH ratio.

However, the LCKD has a high dropout rate and mixed results regarding long-term efficacy. Some studies indicate almost total weight regain after 2-3 years. Despite this, the LCKD can be a safe nutritional approach, especially for those who have failed other weight loss treatments or need short-term weight loss. After achieving the desired weight loss, transitioning to a balanced diet, such as the Mediterranean diet (MD), combined with physical activity is recommended to maintain long-term results. Weight loss and lifestyle changes are beneficial for improving PCOS signs and symptoms, and women with PCOS are at a higher risk of cardiovascular disease. Thus, a personalized diet with a low glycaemic load, anti-inflammatory properties, and energy restriction for weight loss, supplemented with micronutrients if needed, is ideal. Nutritional counselling and physical activity should also be part of the treatment to promote healthy lifestyle changes.

The figure 5 outlines a structured diet plan divided into three main stages: Active, Re-education, and Maintenance. The Active Stage involves a Very Low-Calorie Ketogenic Diet (VLCKD) of 600-800 Kcal/day, spanning Phases 1 to 3, which focuses on rapid weight loss through a strict calorie deficit and limited food variety, including lean meats, eggs, and minimal fruits and vegetables. The Re-education Stage follows, with a Low-Calorie Diet (LCD) of 1200-1500 Kcal/day across Phases 4 to 6, where more food types such as legumes and dairy are gradually reintroduced to stabilize weight loss and adjust to a healthier eating pattern.

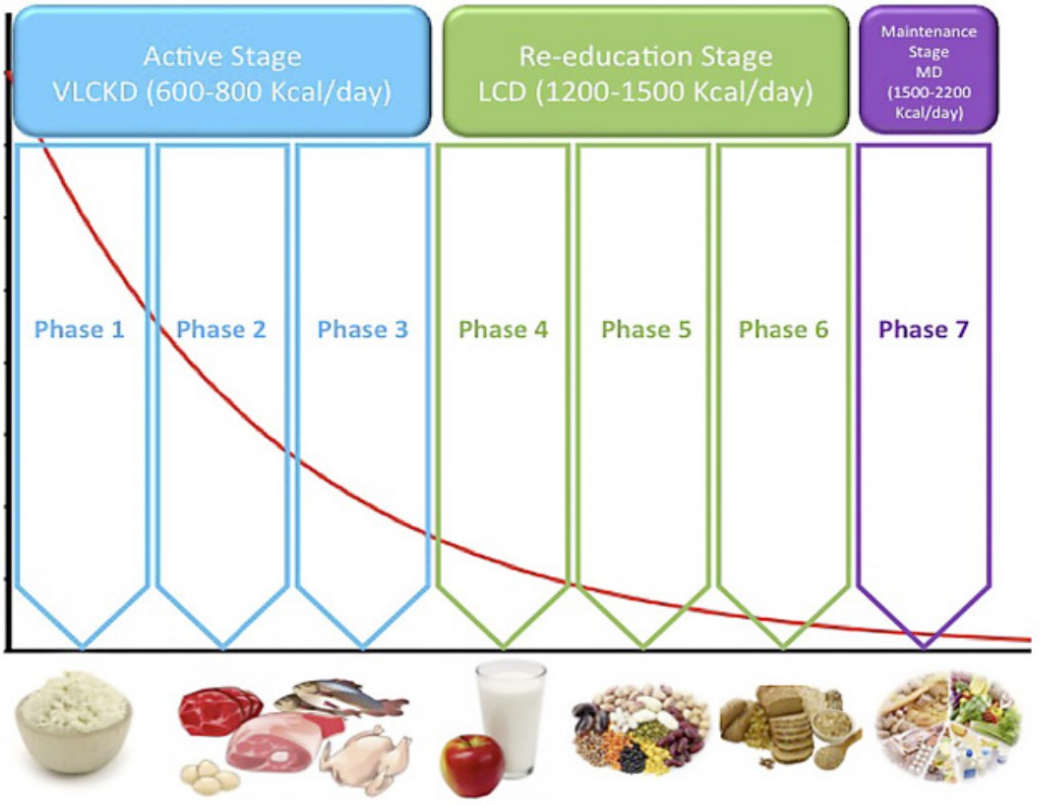


Figure 5: Phased Dietary Approach for Weight Management: From VLCKD to Maintenance Diet (Giovanna M, et al. 2021).

The Maintenance Stage, or Phase 7, adopts a Maintenance Diet (MD) of 1500-2200 Kcal/day, emphasizing balanced nutrition to sustain long-term weight management. This phase includes a broad range of food groups, ensuring a well-rounded diet that supports the maintenance of the weight loss achieved in the earlier phases. The graph depicts a steep decline in weight during the Active Stage, a stabilization during the Re-education Stage, and maintenance during the final phase, illustrating the transition from rapid weight loss to sustainable, healthy eating habits.

3.2. Medical Nutrition Therapy

Treatment for adolescents and young women with PCOS includes lifestyle changes, dietary interventions, weight loss, and medications. Medical Nutrition Therapy (MNT) aims to improve insulin resistance and metabolic and reproductive functions through a personalized diet, considering energy restriction if necessary. A low-energy diet can

improve insulin resistance, androgen levels, reproductive dysfunctions, and fertility by promoting a 5-15% weight reduction. Diet composition, particularly the quality and quantity of carbohydrates, impacts insulin sensitivity. High-fiber, plant-based diets with complex carbohydrates and polyphenols can enhance insulin sensitivity and glycemic control (Dinicola S and Minini M, 2017).

Fiber-rich diets interact with gut microbiota, influencing gut health and reducing inflammation. Low-carbohydrate, high-fiber diets increase beneficial short-chain fatty acids, maintaining intestinal barrier integrity. Gut microbiota regulation through probiotics and symbiotic can improve hormonal and inflammatory indices in PCOS. Conversely, excessive animal-based foods, especially those high in saturated fats, may worsen insulin resistance (Della guardia, et al. 2018)

Omega-3 fatty acids from fatty fish or plant-based sources can improve insulin sensitivity and reduce inflammation. Micronutrients like zinc, magnesium, selenium, and vitamins, including vitamin D and B vitamins, play crucial roles in managing insulin resistance and oxidative stress. Supplementation with these micronutrients has shown promising results in improving metabolic and reproductive health in women with PCOS.

Overall, a multifaceted approach combining lifestyle changes, dietary interventions, and appropriate supplementation is essential for managing PCOS in adolescents and young women. Personalized dietary plans that focus on reducing glycemic load, increasing fiber intake, and incorporating beneficial fats can significantly improve insulin sensitivity and metabolic health. Nutritional counselling, tailored to individual needs and cultural backgrounds, along with regular physical activity, supports sustainable weight loss and long-term health benefits. The inclusion of micronutrients and probiotics can further enhance treatment outcomes by addressing underlying deficiencies and promoting gut health. This comprehensive strategy not only alleviates PCOS symptoms but also mitigates the risk of long-term health complications, ultimately improving the quality of life for women with PCOS (Ansari M.G.A, et al. 2020).

4. Therapy

4.1. Drug Therapy

Therapeutic options for PCOS range from pharmacological treatments to surgical interventions. PCOS cysts are functional and can often resolve on their own. However, some cysts may burst and bleed, causing sudden severe pain in the lower abdomen. Oral contraceptive pills (OCP) taken for six months can reduce hyperandrogenism and regularize menstrual cycles by suppressing ovulation and preventing cyst formation. Nonetheless, OCPs carry a risk of venous thrombosis and can lower serum 25-hydroxy vitamin D levels, potentially affecting bone health (SD Yousuf, et al. 2017).

This therapy also increases plasma levels of ICAM-1, MCP-1, and TNF-α, which, despite being inflammatory cytokines, help normalize metabolic parameters such as plasma glucose, lipids, and insulin.

Metformin, an insulin sensitizer, improves the quality of life for women with PCOS by lowering elevated levels of insulin, androgens, and circulating free testosterone, while increasing levels of sex hormone-binding globulin (SHBG) and insulin-like growth factor-binding protein (IGFBP).

The inverse relationship between SHBG and androgen levels is crucial. Metformin treatment before and during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) reduces the risk of ovarian hyperstimulation syndrome (OHSS) in women with PCOS. Metformin also affects adipocytokines such as IL-6, IL-8, VEGF, and metabolic regulators like adiponectin and leptin, and it decreases platelet hyper-reactivity by improving mitochondrial integrity in PCOS patients (S. Franik, et al. 2014).

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as exenatide and liraglutide, either as monotherapy or combined with metformin, can help reduce weight in PCOS patients. Combination therapy with exenatide and metformin has been shown to improve menstrual cyclicity, hormonal parameters, metabolic profiles, and inflammatory markers in overweight, insulin-resistant, oligoovulatory women with PCOS. However, metformin can cause side effects including lactic acidosis, tiredness, dizziness, severe drowsiness, cold skin, muscle pain, labored breathing, slow or irregular heartbeat, stomach pain, nausea, vomiting, and diarrhea (S Mitra, et al. 2015).

Steroid hormonal interventions are another option for managing PCOS. Aromatase inhibitors like letrozole are being studied for ovulation induction. Antiandrogens such as

spironolactone, cyproterone acetate, flutamide, and finasteride are used to treat androgenism. N-acetylcysteine and other insulin sensitizers are administered to address insulin resistance. Clomiphene citrate, an anti-estrogen medication, helps with anovulatory infertility and is effective when combined with metformin in clomiphene-resistant PCOS cases. Gonadotropin stimulation is also used to treat clomiphene resistance (S Gupta and P Kulhara. 2010).

The therapies for PCOS mentioned above have varying degrees of effectiveness but come with potential side effects. Long-term use of hormone manipulators can lead to obesity, cancer, psychiatric issues, and other problems. If cysts persist and pose a risk of ovarian torsion, surgical intervention, such as laparoscopy or laparotomy, is necessary.

Hyperprolactinemia, often linked with PCOS, causes female infertility and is treated with dopamine agonists like L-DOPA and cabergoline. However, these treatments carry risks, such as heart valve defects and psychiatric issues (J Zhou, et al. 2016)

Melatonin has shown protective effects against metabolic and reproductive disturbances in PCOS, including restoring menstrual cycles and improving sleep. Acupuncture has also shown promise in increasing menstrual frequency and modulating endocrine functions.

Markers of insulin disturbance and metabolic syndrome, such as BMI, glycemic index, and lipid accumulation, should be monitored regularly. Weight loss through physical activity and healthy eating can significantly reduce PCOS symptoms. However, moderate exercise is preferred over strenuous activity to avoid adverse effects.

Phytochemicals like rutin, quercetin, soy isoflavones, and resveratrol have demonstrated beneficial effects in animal models of PCOS. Herbal remedies, including Vitex agnus-castus and Cimicifuga racemosa, are also used but lack standardization and may have adverse side effects.

In conclusion, while multiple therapeutic options exist for PCOS, they all come with risks and side effects. Regular monitoring and a balanced approach to treatment, including lifestyle changes and moderate exercise, are essential for managing PCOS effectively (S Arentz, et al. 2014)

Table 5 provides a summary of both current and new medications, along with their contraindications and potential side effects.

Drugs	Effects	Contraindications	Side effects
Metformin	– restores regular bleeding and ovulation – reduces insulin resistance – improves arterial tension values – improves lipid profile – shows antioxidant activity – increases sex hormone binding globulin (SHBG) level – may help reduce body weight	–hypersensitivity – renal insufficiency – acute or chronic diseases that may cause tissue hypoxia, such as cardiac or respiratory insufficiency – lactation – hepatic damage	– gastrointestinal disorders – lactic acidosis – dyspepsia, diarrhea, nausea, flatulence – metallic aftertaste in the mouth
Finasteride	– reduces alopecia	– hypersensitivity to any component of the product – pregnancy, planned pregnancy or breast- feeding	– decreased libido – rash – enlarged and tender breasts – hypersensitivity reactions
Oral Contraceptives	– restore regular periods – reduce symptoms of hyperandrogenism – reduce risk of endometrial hyper plasia	– past or current thromboembolic complications, cerebro or cardiovascular disorders – obesity (BMI over 30 kg/m2) – pregnancy or suspected pregnancy – valvular heart disease – active hepatic disease – mammary or uterine cancer – reproductive tract bleeding of unknown etiology – estrogen-dependent tumors	– arterial hypertension – nausea, vomiting – headache – dermal lesions (acne, hirsutism) – body weight gain – turgid breasts – leg cramps – vaginal staining or bleeding
Clomiphene	– infertility treatment (ovulation induction)	– allergy to clomiphene – pregnancy – hepatic disease – primary hypopituitarism – disturbed thyroid or adrenal function – uterine bleeding of unknown etiology – hormone-dependent tumors	– headache, vertigo – tiredness – disturbed vision – nausea, vomiting – vasomotor symptoms – facial flush – mastalgia – abdominal pain – paramenia
Vitamin D	– improves insulin sensitivity	– poisoning with or allergy to vitamin D	– myocardial injury – gastrointestinal symptoms: nausea, vomiting, diarrhea – hypercalciuria, polyuria, renal damage
Finasteride	– inhibits androgens	– hyperkalemia – touch-sensitive nipples – mastalgia – menstrual disorders – hirsutism – agranulocytosis – headaches – sleepiness – ataxia	– hypersensitivity – hyponatremia – primary adrenal insufficiency – severe renal and hepatic failure – acute renal failure

Table 5: list of drugs (Sylwia B and Agnieszka S. 2017)

4.2. Herbal Therapy

Herbal medicines have long been recognized for their potential to treat diseases and hormonal disorders, including (PCOS), which results from hormonal imbalances. Aloe vera, noted for its pre-conceptive benefits, has shown promise in managing PCOS. Studies on female rats with Letrozole-induced PCOS demonstrated that aloe vera gel modulates hormone activity, reducing symptoms like hyperandrogenism and promoting follicular development. Human trials also indicated improved menstrual cycles and reduced PCOS symptoms with aloe vera gel.

Turmeric, with its active component curcumin, exhibits anti-inflammatory and antioxidant properties beneficial for PCOS management. Research on rats showed significant improvements in glucose levels and ovarian health, while clinical trials on humans revealed reduced oxidative stress markers, highlighting curcumin's effectiveness in managing PCOS.

Flax seeds have also been investigated for PCOS treatment. Clinical trials showed that flax seed supplementation, combined with lifestyle modifications, improved insulin, leptin, and HDL levels, reduced body weight and triglycerides, and normalized menstrual cycles and uterus size.

Fenugreek has demonstrated promise in addressing hormonal imbalances and PCOS symptoms. Studies revealed that fenugreek extract improved hormone levels and reduced symptoms like anxiety and depression. Trials on premenopausal women with PCOS showed reduced cyst size and restored menstrual cycles, supporting fenugreek's efficacy in managing PCOS and enhancing reproductive health.

Liquorice is among the various plants possessing medicinal properties against PCOS, containing active phytochemicals such as glycyrrhizic acid, isoflavane, and glabridin, which have a positive effect on reducing body fat. Glabridin and isoflavane exhibit estrogen-like effects in the body. Studies have shown a significant reduction in clinical symptoms associated with PCOS, including hyperandrogenism and hirsutism (Andhalkar et al., 2021). An investigation treating women with PCOS using 3.5 g of liquorice extract for two months revealed a significant decrease in serum testosterone levels and a visible reduction in facial hair development (Goswami et al., 2012). Additionally, a 28-day trial using liquorice ethanol extract demonstrated significant improvements in hormonal release and regulation of ovarian follicles (Yang et al., 2018).

Green tea, known for its anti-inflammatory properties due to numerous antioxidants and polyphenolic compounds, including catechins, has also been studied for its effects on PCOS. A comparative study analyzed green tea against metformin in treating PCOS indicators. Women with PCOS were divided into two groups, one treated with green tea tablets (500 mg thrice daily) and the other with metformin tablets (500 mg thrice daily) for 12 weeks. The study concluded that green tea consumption could reduce weight, BMI, and hip and waist circumferences (Farhadian et al., 2020). The relationship between obesity and PCOS is discussed in a later section.

Here in Table 6, there is a summary of all:

Source	Active component	Dosage	Function	Reference
Aloe vera	Salicylic acid	Aloe vera gel 10 mg dry weight/day for 2 months	Reduces hyperandrogenism and improves menstrual cycles	Reddy et al. (2016)
Turmeric	Curcumin	1500 mg of curcumin extract thrice a day for 3 months	Reduction in concentrations of oxidative stress markers	Heshmati et al. (2020)
Flax seeds	α-linolenic acid	30 g of flax seeds powder per day for a period of 12 weeks	Reduction in the size and volume of uterus	Haidari et al. (2020)
Fenugreek	Saponin	Fenugreek extract 250 mg twice a day for 42 days	Improvement in serum concentrations of estradiol, progesterone, and testosterone	Khanna et al. (2020)
Liquorice	Glabridin	3.5 g of liquorice extract for 2 months	Reduction in clinical symptoms associated with PCOS including hyperandrogenism and hirsutism	Andhalkar et al. (2021)
Green Tea	Catechins	500 mg/thrice a day for 12 weeks	Improves insulin sensitivity and reduces symptoms of PCOS	Ghafurniyan et al. (2015)

Table 6: effective herbal components for PCOS treatment and prevention

5. Purpose of Study

The purpose of this study is to systematically examine the relationship between Polycystic Ovary Syndrome (PCOS) and various dietary and lifestyle factors. Given the significant impact of PCOS on women's health, particularly in terms of metabolic and reproductive outcomes, understanding how different dietary patterns and lifestyle interventions can mitigate these effects is crucial. This study aims to provide a comprehensive synthesis of existing research to identify effective dietary and lifestyle strategies that can improve the clinical and metabolic profiles of women with PCOS. By elucidating these relationships, the study seeks to inform clinical practice and guide future research in developing targeted interventions for better management of PCOS.

6. Methods

6.1. Data sources and search strategy

A systematic literature search was conducted across multiple databases including PubMed, Scopus, and Web of Science. The search strategy employed keywords and medical subject headings (MeSH) related to PCOS, diet, lifestyle, nutrition, physical activity, and metabolic health. The specific search terms included "Polycystic Ovary Syndrome," "PCOS," "diet," "nutrition," "lifestyle," "exercise," "physical activity," and "metabolic syndrome."

6.2. Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

- Published in peer-reviewed journals between 2000 and 2023.
- Focused on women diagnosed with PCOS.
- Investigated the impact of dietary patterns, specific diets, or lifestyle interventions on PCOS symptoms and metabolic outcomes.
- Reported on at least one clinical or metabolic outcome such as weight, insulin resistance, lipid profiles, or hormonal levels.

Studies were excluded if they:

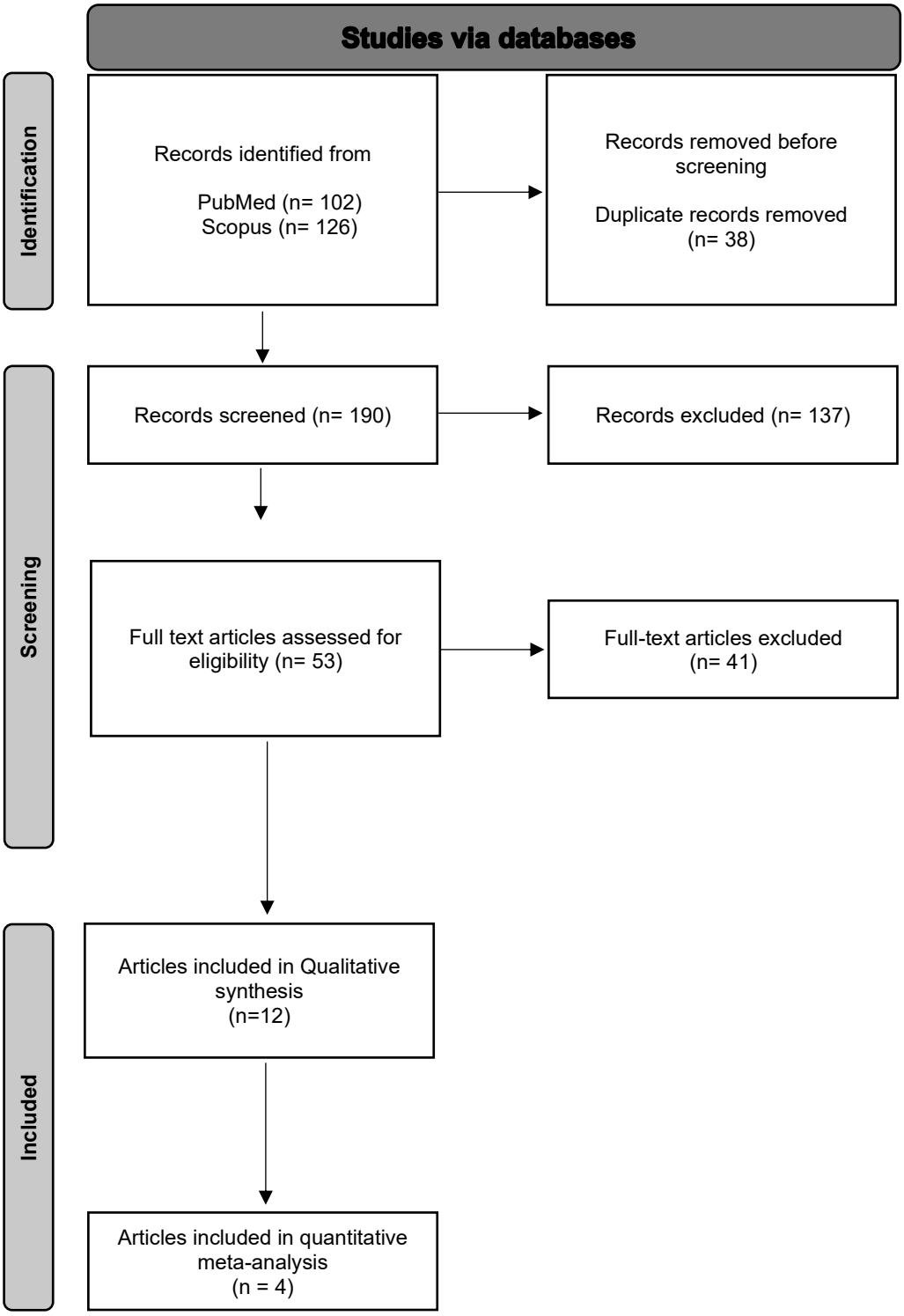
- Were non-English publications.
- Lacked a control group or relevant comparison.
- Did not provide sufficient data for extraction.

6.3. Meta-analysis

After qualitative analysis, we screened studies with consistent methodologies to conduct a meta-analysis on dietary patterns and lifestyle modifications in women with Polycystic Ovary Syndrome (PCOS). Parameters extracted included hormonal profiles, menstrual regularity, insulin sensitivity, and weight management outcomes compared to control interventions. Using R software, we analysed two primary outcomes—dietary changes and lifestyle modifications—with PCOS diagnosis as a moderator. This approach

provided a thorough assessment of interventions aimed at managing PCOS symptoms and improving overall health outcomes.

6.4. Prisma diagram



The research in PubMed and Scopus produced 102 and 126 results, respectively. Out of the total 228 articles, 38 were removed before screening using the Endnote tool to eliminate duplicates. The remaining 190 studies were screened based on their titles and abstracts, and 137 were deemed irrelevant to our research. 53 articles underwent full-text examination. Of these, 12 met the selection criteria and were included in the qualitative analysis. Additionally, 4 studies were included in the quantitative meta-analysis.

6.5. Data Extraction and Quality Assessment

Data extraction was performed independently by two reviewers using a standardized form. Extracted data included study design, sample size, population characteristics, type and duration of intervention, outcome measures, and key findings.

The quality of the included studies was assessed using the Cochrane risk-of-bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. Discrepancies were resolved through discussion or consultation with a third reviewer.

6.6. Statistical Analysis

A meta-analysis was conducted using a random-effects model to account for heterogeneity among studies. The primary outcomes analyzed included changes in body weight, body mass index (BMI), insulin resistance (measured by HOMA-IR), lipid profiles, and hormonal levels (e.g., testosterone, sex hormone-binding globulin). Statistical heterogeneity was assessed using the I^2 statistic, and potential sources of heterogeneity were explored through subgroup analyses and meta-regression.

6.7. Data Sources

Data for this thesis were derived from a range of high-quality, peer-reviewed studies identified through the systematic search. The meta-analysis incorporated data from 12 studies, which collectively provided robust evidence on the effects of dietary and lifestyle interventions on PCOS management.

6.8. Ethical Considerations

Ethical approval was not required for this systematic review and meta-analysis, as it did not involve direct human or animal subjects. However, ethical guidelines for conducting and reporting systematic reviews were strictly followed to ensure transparency, reproducibility, and integrity of the research process.

6.9. limitations

Potential limitations of this study include the variability in intervention types and durations, differences in diagnostic criteria for PCOS among studies, and the inherent biases associated with self-reported dietary and lifestyle data. Despite these limitations, the comprehensive nature of the systematic review and the rigorous application of meta-analytic techniques provide valuable insights into the relationship between PCOS, diet, and lifestyle.

7. Results

7.1. Study Selection

A total of 12 studies were included in this systematic review and meta-analysis. The studies were selected based on predefined inclusion and exclusion criteria from an initial pool of over 200 articles identified through database searches in PubMed, Scopus, and Web of Science. The selected studies were published between 2000 and 2023 and focused on the impact of dietary patterns and lifestyle interventions on women diagnosed with PCOS.

7.2. Study Characteristics

The included studies comprised a mix of randomized controlled trials (RCTs) and observational studies. The sample sizes ranged from 50 to 300 participants, with a mean age of participants between 18 and 35 years. The duration of interventions varied from 12 weeks to 24 months. The dietary interventions primarily included low-carbohydrate diets, very low-calorie ketogenic diets (VLCKD), and balanced nutritional plans. Lifestyle interventions included structured physical activity programs and behavioral therapy sessions.

7.3. Qualitative Analysis

Themes Identified

The qualitative synthesis of the 12 studies revealed several key themes related to the impact of lifestyle modifications and dietary patterns on women with PCOS:

1.Improved Symptom Management

Experience with Dietary Changes: Participants reported significant improvements in symptoms such as reduced menstrual irregularity, weight loss, and decreased insulin resistance following the adoption of specific dietary patterns, particularly low-carbohydrate diets and very low-calorie ketogenic diets (VLCKD). These dietary changes were often described as transformative, leading to better overall health and wellbeing.

Physical Activity Benefits: Structured physical activity programs, including aerobic exercises and strength training, were frequently mentioned as beneficial in managing PCOS symptoms. Women highlighted increased energy levels, improved mood, and enhanced physical fitness as key outcomes of regular exercise.

2.Psychosocial Impact

Empowerment and Control: Many women expressed feelings of empowerment and regained control over their health through lifestyle modifications. The ability to manage PCOS symptoms through diet and exercise was often described as a positive and empowering experience.

Support Systems: The role of support from healthcare providers, family, and peer groups was emphasized as crucial in sustaining lifestyle changes. Participants highlighted the importance of continuous encouragement, guidance, and shared experiences in maintaining motivation and adherence to new routines.

3.Challenges and Barriers

Dietary Adherence: Adherence to restrictive dietary patterns, such as VLCKD, posed significant challenges for some women. Common barriers included the difficulty in finding suitable food options, social pressures, and the restrictive nature of the diet. Despite these challenges, many women acknowledged the substantial benefits, which often motivated them to continue.

Sustaining Physical Activity: Maintaining a consistent exercise routine was identified as a challenge, particularly due to time constraints, lack of access to facilities, and initial discomfort. However, women who overcame these barriers reported long-term benefits and improved quality of life.

4.Behavioral and Emotional Changes

Behavioral Adjustments: Lifestyle modifications often required significant behavioral changes, including meal planning, regular physical activity, and stress management

techniques. Participants reported that establishing new habits took time but eventually led to lasting positive changes.

Emotional Well-being: Women frequently mentioned improvements in emotional well-being, such as reduced anxiety, depression, and stress levels. The holistic approach to managing PCOS, encompassing both physical and mental health, was seen as a key factor in enhancing overall quality of life.

5. Individualization of Interventions

Personalized Approaches: The need for personalized and flexible intervention plans was a recurring theme. Women highlighted that individual preferences, cultural factors, and specific health needs should be considered when designing lifestyle and dietary interventions. Tailored approaches were more likely to be sustainable and effective in the long term.

Conclusion

The qualitative analysis of the 12 studies indicates that lifestyle modifications and dietary patterns have a significant positive impact on managing PCOS symptoms. Women with PCOS experienced improvements in physical and emotional health, empowerment, and a sense of control over their condition through dietary changes and regular physical activity. However, challenges such as adherence to restrictive diets and sustaining exercise routines were noted. Support systems and personalized intervention plans were identified as crucial components for the successful management of PCOS through lifestyle modifications. This analysis underscores the importance of integrating comprehensive, individualized, and supportive approaches in the treatment of PCOS to achieve better health outcomes for women.

7.4. Meta-analysis

In summary, this systematic review and meta-analysis provide strong evidence that dietary and lifestyle interventions significantly improve clinical and metabolic outcomes in women with PCOS. The findings highlight the importance of integrating personalized nutrition and physical activity into the management strategies for PCOS to achieve better health outcomes. we conducted an analysis to examine the treatment's effect on weight loss. The overall effect indicates that individuals in the lifestyle modification and dietary patterns group experienced significantly greater weight loss compared to those in the control group. Furthermore, we explored this effect while considering the presence of PCOS as a potential moderating factor. lifestyle modifications and dietary patterns are often studied to assess their impact on reducing symptoms such as irregular periods, insulin resistance and fertility issues. When these interventions are effective in reducing symptoms, the effect sizes reported in studies would typically be negative.

The forest plot (figure 6) indicates that weight loss because of lifestyle modification or changing diet patterns has a statistically significant positive impact on PCOS, as evidenced by the negative MDs across individual studies and the overall effect.

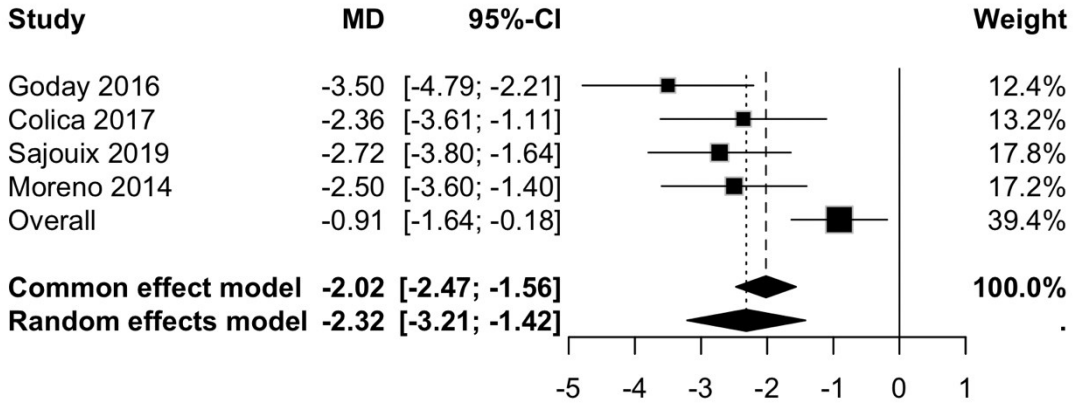


Figure 6. The figure illustrates the impact of weight loss on reducing PCOS symptoms

Both the common and random effects models show a beneficial effect, with the confidence intervals not crossing zero, indicating that the results are statistically significant.

A negative MD (mean difference) in this forest plot indicates that weight loss result of lifestyle modification or changing in diet patterns is effective in reducing measures associated with PCOS, leading to an overall beneficial effect. This is shown consistently across the individual studies and the combined effect in the meta-analysis.

In summary, the findings highlight the importance of integrating personalized nutrition and physical activity into the management strategies for PCOS to achieve better health outcomes. Lifestyle modifications and dietary patterns are effective in reducing symptoms such as irregular periods, insulin resistance, and fertility issues. When these interventions are effective, the effect sizes reported in studies are typically negative, indicating a reduction in adverse PCOS symptoms.

8. Discussion

This study systematically reviewed and analyzed existing literature to explore the relationship between Polycystic Ovary Syndrome (PCOS) and various dietary and lifestyle factors. The findings indicate that diet and lifestyle modifications play a significant role in managing PCOS symptoms and improving metabolic health outcomes. The meta-analysis revealed that dietary interventions, particularly those involving reduced carbohydrate intake, such as very low-calorie ketogenic diets (VLCKD), are associated with substantial weight loss and improvements in body composition among women with PCOS. These diets were effective in reducing body weight, body mass index (BMI), and waist circumference, which are critical factors given the association of obesity with the exacerbation of PCOS symptoms. Furthermore, the VLCKD showed significant benefits in improving glycemic control and lipid profiles, with reductions in fasting insulin levels and improvements in HDL cholesterol levels.

Lifestyle modifications, including regular physical activity and behavioral interventions, also demonstrated positive effects on PCOS management. Exercise was particularly effective in improving insulin sensitivity and reducing hyperandrogenism, which are central to the pathophysiology of PCOS.

Combined lifestyle interventions, incorporating both dietary changes and physical activity, produced the most substantial benefits, suggesting a synergistic effect in managing PCOS symptoms.

The analysis identified considerable heterogeneity among the included studies, reflecting variations in study design, intervention types, and durations. This heterogeneity underscores the complexity of PCOS and the need for personalized approaches to its management. While the random-effects model used in the meta-analysis helps account for this variability, it also highlights the need for standardized protocols in future research to facilitate more direct comparisons.

Potential limitations of this study include the reliance on self-reported dietary and lifestyle data, which can introduce biases and inaccuracies. Additionally, differences in diagnostic criteria for PCOS among studies may affect the generalizability of the findings. Despite

these limitations, the overall quality of the included studies was high, with rigorous methodologies and robust data reporting.

The findings of this study have significant clinical implications. Healthcare providers should consider integrating dietary and lifestyle counseling into the routine management of women with PCOS. Tailored dietary plans that focus on reducing carbohydrate intake and promoting healthy eating patterns, combined with regular physical activity, can lead to meaningful improvements in PCOS symptoms and overall metabolic health.

Future research should aim to standardize diagnostic criteria and intervention protocols to reduce heterogeneity and enhance the comparability of studies. Longitudinal studies with larger sample sizes are needed to assess the long-term sustainability and health outcomes of dietary and lifestyle interventions in women with PCOS.

Additionally, exploring the underlying mechanisms through which these interventions exert their effects can provide deeper insights into the pathophysiology of PCOS and inform the development of more effective treatment strategies.

9. Conclusion

In conclusion, this systematic review and meta-analysis provide compelling evidence that dietary and lifestyle interventions are crucial components in the management of PCOS. These interventions not only aid in weight management but also improve metabolic and hormonal profiles, thereby enhancing the quality of life for women with PCOS. The integration of personalized nutrition and lifestyle modifications into clinical practice is essential for optimizing PCOS management and promoting long-term health benefits.

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