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Review Article

Nutraceutical-Based Management of Polycystic Ovary Syndrome : An Updated Review

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ABSTRACT

This article looks at Polycystic Ovary Syndrome (PCOS) including how prevalent globally it is. It also looks at the causes and risk factors of PCOS. PCOS can lead to insulin resistance, high levels of androgens, infertility and metabolic problems. This article discusses lifestyle changes, Hormonal therapy and alternative treatments. It stresses that treatment should be tailored to each individual and further research to help improve women's health.

INTRODUCTION

3.1 Overview of PCOS:

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of reproductive age. It affects women from adolescence to post-menopause. The prevalence of PCOS is 10-13%. PCOS has a complex aetiology with heterogenous presentations. It can present with reproductive, metabolic and psychological features (Teede et al., 2010; Azziz et al.,

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2016). Women internationally suffer from delayed diagnosis and are dissatisfied with their care .There is inconsistency in clinical practice when assessing and managing PCOS. The 2018 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome was independently assessed to have high quality. This extensive update has incorporated current literature, previous systematic reviews and new consumer prioritised clinical questions. Our aim is to update and expand on evidence-based guidelines to provide rigorous and comprehensive evidence to improve the lives of those with PCOS worldwide. This was achieved by utilising substantial investment from government and societies. It has involved extensive consumer engagement and international collaboration with leading societies and organisations, multidisciplinary experts and primary care representatives. This comprehensive evidence-based guideline has been developed using rigorous Appraisal of Guidelines for Research and Evaluation-II (AGREEII) compliant processes. It provides a single source of international evidence-based recommendations to guide clinical practice. It can be adapted to relevant health systems. This guideline has been accompanied by an extensive translation plan to reduce variability in care worldwide. It aims to provide high quality clinical services to improve health outcomes and quality of life for women with PCOS. The guideline has been supported by a multi-faceted international translation plan with co-designed resources to improve healthcare professionals' skills and empower women with PCOS. An integrated comprehensive evaluation plan has also been implemented. Below we have summarised recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of PCOS.(1)

3.2 Epidemiology and prevalence:

PCOS is a common endocrine disorder affecting 5-10% of fertile women worldwide. Knowing how prevalent PCOS is can help healthcare systems provide effective resources for diagnosis, management and therapy. PCOS is linked to several health risks including obesity, endometrial cancer, type 2 diabetes, infertility and cardiovascular disease. Knowing the epidemiology of a disease can help public health interventions to target reducing these risks.The prevalence and presentation can vary between groups due to genetic, environmental and lifestyle factors. By analysing the global epidemiology we can understand how they differ and tailor interventions to specific groups. PCOS is often misidentified or mis-diagnosed due to variable presentations and lack of consistent diagnostic criteria. Knowing the epidemiology can help improve and refine diagnostic criteria. PCOS is a major cause of female infertility. Knowing the epidemiology of infertility can help identify women at risk so timely interventions can be put in place to improve reproductive outcomes.(2)

Etiology and Risk Factors: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting up to 15% of women of reproductive age. It can lead to reproductive and metabolic dysfunction. There are varied symptoms between different ethnicities. In order to be diagnosed with PCOS according to the Rotterdam criteria you must have 2 of the 3 following diagnostic features: hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphology (PCOM). This results in 4 phenotypes (A-D). The 2018 International Evidence Based Guidelines highlight the importance of early diagnosis of PCOS, complications with metabolism and psychological difficulties and the need for long-term management.(3)

4. Overview of Nutraceuticals

The term Nutraceutical was created in 1989 by Stephen DeFelice MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ. It is derived from the words Nutrition and Pharmaceutical. 1 DeFelice defined Nutraceutical as "Food (or parts of food) that confers medical or health benefits, including the prevention and/or treatment of disease". However, the term nutraceutical does not have any official definition in marketing. I would like to propose that we redefine what Functional Foods and Nutraceuticals are. If food is cooked/produced with scientific intelligence (Whether we know how and why or not), this is called Functional Food. Functional food will therefore provide the correct amount of vitamins, fats, proteins, carbohydrates etc to the body to survive healthily. Supplementing with Nutraceuticals or specific micronutrients has been identified as a beneficial adjuvant

therapy to lifestyle and/or pharmaceutical treatments to manage chronic diseases such as PCOS. Although there is no universal definition of Nutraceuticals, they have previously been described as nutrient derivatives or plant, animal or food extracts that may elicit a pharmacological effect. Evidence suggests women with PCOS actively seek out complementary medicines (CM) to manage their PCOS symptoms. A previous cross-sectional study involving 493 Australian women with PCOS found that over 70% of women had used some form of CM within the last 12 months. Micronutrient supplementation included Vitamin, Mineral, Fish Oil Capsules and Herbal Supplementation. Almost one third of women felt CM had therapeutic benefits to manage their PCOS symptoms and very few women reported negative effects of nutritional/Herbal supplements. Previous systematic reviews have shown mixed results regarding the effectiveness of Nutraceutical/ Micronutrient supplementation, in improving PCOS symptoms. Differences in study design, sample size, population and adequate controls have been reported as limitations. To date, clinical practice guidelines and higher level evidence have focussed on the effectiveness of multi-modal lifestyle interventions (Diet and Physical Activity) to manage PCOS but have not specifically mentioned any specific nutrients. Due to the rapidly increasing use of nutritional supplementation to manage features of PCOS, a synthesis of higher level evidence is warranted. However, due to the large volume of evidence, undertaking a systematic scoping review will allow us to identify and summarise the current literature. The purpose of this scoping review was to identify the type and frequency of Nutraceutical/Micronutrient supplementation used to manage features of PCOS (Anthropometric, Metabolic, Reproductive and Psychological). This review highlights the breadth of evidence currently available, and identifies gaps in the literature to inform future research. Including primary research, systematic reviews and meta-analyses.(4)

5. PATHOPHYSIOLOGY OF PCOS

5.1 Neuroendocrine Disruption

PCOS is associated with a disruption of the normal control of the reproductive hormones. There's an increased pulsatile secretion of GnRH and reduced negative feedback from the sex hormones resulting in a raised LH:FSH ratio. The high levels of LH stimulate the theca cells in the ovary to produce excessive androgens and the low levels of FSH will have an effect on the development and maturation of the follicles (leading to follicular arrest) and this can in turn lead to anovulation.

Kisspeptin-producing neurons, particularly KNDy neurons, play an important role in regulating GnRH secretion. Altered kisspeptin activity has been observed in women with PCOS and may contribute to hormonal imbalances, although the exact mechanism is not fully understood. Other regulatory factors, including neurokinin B and dynorphin, also influence GnRH secretion by stimulating or inhibiting its release. Additionally, changes in gamma-aminobutyric acid (GABA) and elevated anti-Müllerian hormone (AMH) levels may affect hormonal regulation, follicular development, and ovulation, further contributing to reproductive abnormalities in PCOS.

5.2 Classical Pathway of Androgen Synthesis

Excess androgen production, known as hyperandrogenism, is one of the major features of PCOS. It is mainly associated with increased LH secretion, the influence of insulin on ovarian hormone production, and increased sensitivity of ovarian theca cells to LH. Androgen synthesis begins with cholesterol, which is converted through a series of enzymatic reactions into dehydroepiandrosterone (DHEA), androstenedione, and testosterone. Hormonal abnormalities in PCOS may also be due to changes in the activity of steroid-metabolizing enzymes. For example, alteration of ovarian activity of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) may influence the regulation of steroid hormones. Increased expression of vascular endothelial growth factor (VEGF) may also stimulate the synthesis of androgens and may result in altered ovarian stromal and thecal tissues. These hormonal and enzymatic changes can interfere with proper follicular growth and ovulation, and thereby worsen the reproductive symptoms associated with PCOS.

5.3 Hyperinsulinism

In Polycystic Ovary Syndrome (PCOS) insulin resistance leads to hyperinsulinaemia, contributing to

hyperandrogenism. Insulin stimulates ovarian androgen production and increases steroidogenesis in the adrenal glands. Insulin promotes increased androgen production through stimulating AKR1C3 in adipose tissue and lowers Sex Hormone Binding Globulin (SHBG) in the blood. This leads to increased levels of free active androgen in circulation. Excess androgen production can cause increased insulin resistance. Hyperandrogenism can increase abdominal and visceral fat deposits causing worsening insulin resistance. Not all women with PCOS will have insulin resistance however studies show that women with PCOS will have reduced insulin sensitivity compared to control subjects. Recent studies have split PCOS into subgroups based on the main source of androgen excess. Some women will have ovarian derived androgen excess whilst others will have adrenal derived androgen excess. There is also a mild androgen excess group. The adrenal related group have been shown to have higher rates of hirsutism, insulin resistance and type 2 diabetes.(5)

5.4 Oxidative Stress in PCOS

Oxidative stress can develop in people with PCOS because of a mix of genetic, environmental, and hormonal influences. Poor mitochondrial function can lead to an excess production of reactive oxygen species, which can harm mitochondrial DNA, proteins, and lipids, eventually causing cell death.A reduction in mitochondrial DNA and the presence of genetic mutations may play a role in causing metabolic problems. Nutritional and inflammatory pathways: Consuming more nutrients, especially glucose, can increase levels of reactive oxygen species. The inflammatory pathway can be activated by the NF-κB process. Higher levels of inflammatory markers like TNF-α and IL-6 are associated with insulin resistance. This has been found in women with PCOS who are at a normal weight. Hormonal factors: High levels of androgens can trigger inflammatory reactions, leading to increased androgen production in the ovaries. This can worsen oxidative stress.Low levels of adiponectin and high levels of free fatty acids can make it harder for the body to store fat.

5.4.1 Effects of oxidative stress in PCOS:

Insulin resistance: The body's ability to take in glucose by muscle and fat tissues is reduced. This leads to lower insulin secretion. Obesity : More fat cells are created. This can affect how the body controls appetite. Hyperandrogenism: Inflammatory substances can boost androgen production in the ovaries.

This can make oxidative stress worse. Follicles: High levels of reactive oxygen species can hinder the development of follicles and lead to cell death.

Proper levels are important for the normal development of egg cells.

Infertility: Oxidative stress can result in poor-quality egg cells. This can make it hard to get pregnant and increase the chance of miscarriage, especially in women who are overweight. In summary, oxidative stress and low-grade inflammation interact with hormonal and metabolic issues, making the symptoms of PCOS more severe.

5.5 Other Implications Due to Oxidative Stress

Vitamin D has an anti-inflammatory and antioxidant effect. By stimulating several pathways (Nrf2) vitamin D can help improve mitochondrial function. This leads to more antioxidants being produced (e.g. glutathione/glutathione peroxidase). Vitamin D supplementation has been shown to help improve markers of oxidative stress. For example, C reactive protein, malondialdehyde and total antioxidant capacity were improved however inconsistencies have been seen. During low glutathione levels, oxidative stress will increase. This will also lead to reduced levels of vitamin D binding protein, hydroxylase and receptors. Research has shown vitamin D and glutathione deficiencies can be associated which can lead to increased inflammatory markers. Osteocalcin can play a role in glucose metabolism and increasing insulin sensitivity. u-OC increases insulin, adiponectin and glucose uptake in muscle tissue. Inconsistencies have been found in osteocalcin levels in the PCOS women. More research is required to understand its association with hyperandrogenism and oxidative stress. Immune dysfunction can also be involved in the pathogenesis of PCOS. Immune cells have been found to be abnormal along with inflammatory markers (C reactive protein) and

immunoglobulins. This means immune dysfunction could be contributing to chronic low-grade inflammation. Overall vitamin D deficiency, altered osteocalcin regulation, oxidative stress and immune dysfunction may all interact with the metabolic and hormonal dysregulation seen in women with PCOS. More research is required to understand the mechanisms and importance.(6)

5.6 Chronic low-grade inflammation in PCOS.

Patients with PCOS can develop chronic low-grade inflammation via genetic, metabolic and environmental factors. Genetic polymorphisms are found in pro-inflammatory cytokine genes such as TNF-a and IL-6. Levels of C-reactive protein (CRP) can be used to measure chronic inflammation. These are mainly produced in the liver in response to stimulation by IL-6. These will be affected by obesity.

- Dietary induced inflammation

Consumption of glucose will cause reactive oxygen species to be formed by mononuclear cells in the blood. This will activate the transcription factor NF-κB increasing pro-inflammatory cytokines (TNF-a and IL-6). Oxidative stress, insulin resistance and potentially atherosclerosis may occur.

- Adipose tissue

Obesity can cause adipose tissue to expand which will cause hypoxia and cell death. This will cause immune cells to be attracted. These cells will differentiate into macrophages. Pro-inflammatory cytokines are formed causing increased insulin resistance. Obese PCOS patients can experience increased inflammation. Healthy weight PCOS women can experience oxidative stress due to glucose.

- Hyperandrogenism

High levels of androgen have been linked to oxidative stress and inflammation. Hyperandrogenism can cause activation of immune cells. Increased glucose sensitivity occurs. Inflammation can cause increased androgen production in the ovaries. This is due to increased CYP17 enzymes and stimulation of theca cell proliferation. This may play a role in the pathophysiology of PCOS. Overall, it appears that chronic low-grade inflammation interacts with oxidative stress, insulin resistance and hyperandrogenism in PCOS patients. This will depend on the weight and metabolism of the patient.(7)

6. Nutraceutical-Based Management of PCOS

6.1 Inositol (Myo-inositol and D-chiro-inositol)

6.1.1 Introduction

Inositol is a naturally occurring carbohydrate like molecule with many roles inside cellular signaling, insulin and reproduction. Whilst inositol is sometimes known as vitamin B8, it is not actually a vitamin as it can be produced by our bodies. The most researched stereoisomers of inositols related to PCOS are Myo-inositol (MI) and D-chiro-inositol (DCI). There are 9 stereoisomers. Polycystic Ovarian Syndrome (PCOS) is commonly associated with insulin resistance and hyperinsulinaemia and this causes excessive androgen production in the ovaries causing menstrual irregularities and problems with ovulation. Inositol has been widely researched due to its role in insulin signaling, glucose metabolism and regulation of ovarian hormones.

6.1.2 Forms and Function of Inositol

It has been reported there are two main inositols that have been researched relating to PCOS management. These are Myo-inositol and D-chiro-inositol [Kalra et al, 2016]. A) Myo-inositol (MI) This is the most common inositol found inside the human body. MI is important in insulin signaling, glucose metabolism and follicle stimulating hormone (FSH) signaling inside the ovaries. This is needed for normal follicular development. Functions: Assists glucose uptake via insulin. Involves ovarian signaling via FSH. Aids follicular development. Aids normal ovarian function. B) D-chiro-inositol (DCI) This is another key stereoisomer of inositol. DCI is formed from Myo-inositol via an insulin dependent epimerisation process. DCI is involved in insulin mediated metabolic pathways and aids glucose utilization. Functions: Involves insulin signaling. Encourages glycogen synthesis. Aids glucose metabolism. Involved with regulating ovarian steroidogenesis.(8)

6.1.3 Mechanism of Action of Myo-inositol and D-chiro-inositol in PCOS

MI and DCI have been shown to provide potential therapeutic benefits in PCOS via their involvement in insulin mediated signalling and ovarian function (Dinicola et al., 2014).

Improves insulin sensitivity

MI and DCI are involved in insulin signalling in the body. Taking supplements may increase insulin sensitivity and glucose uptake in the body. Regulation of androgen secretion Hyperinsulinemia can cause excess androgen secretion from ovarian theca cells. Increasing insulin sensitivity will help regulate the excess androgen secretion from the ovaries. Regulation of follicular development MI is involved in FSH mediated signalling in granulosa cells in the ovary. This helps follicles develop.

Regulation of glucose metabolism DCI is involved in insulin mediated pathways regulating glucose uptake and glycogen synthesis.

Maintains MI/DCI ratio MI and DCI play complimentary roles in the body. The ratio between MI and DCI is considered important for maintaining normal ovarian function and regulation of metabolism.(9)

6.1.4 Role of Inositol in the Management of PCOS

Inositol supplementation has been studied as a nutraceutical intervention for several metabolic and reproductive issues that occur in PCOS. According to a systematic review and meta-analysis by Fitz et al. (2024), inositol supplementation may be beneficial to some metabolic and hormone-related parameters. However, the strength of evidence varies between different outcomes.

Potential benefits are: Improved insulin sensitivity and improved glucose metabolic parameters. Improvement in hormone-related issues due to androgen problems. Improvement in menstrual regularity. Supporting normal follicle development and ovulation. Improvement in fasting insulin and other metabolic parameters. However, there is not enough evidence to determine that there are consistent benefits to all PCOS symptoms.(10)

Myo-inositol alongside D-chiro-inositol The combination of MI and DCI has become an interesting area in research, due to the complementary physiological roles they play. MI primarily plays a role in FSH mediated ovarian signalling whilst DCI plays a role in glucose metabolism and glycogen synthesis via insulin. A study looking at various ratios of MI/DCI supplementation in women with PCOS showed that combining MI and DCI together in a 40:1 ratio was associated with positive outcomes on ovulatory and hormonal parameters. This combination has therefore garnered some interest as a possible nutraceutical approach to address the metabolic and reproductive anomalies associated with PCOS. However, further clinical research is needed in order to establish the most appropriate ratio, dose and length of treatment.(11)

Clinical Evidence A systematic review and meta-analysis was performed of 30 studies (n=2230) to assess the effectiveness of inositol supplementation in PCOS patients. It was found that inositol may have benefits on some metabolic and hormonal biomarkers however the evidence was of low certainty. There is a need for more high quality RCTs. This review showed there was a lot of heterogeneity between studies regarding inositol type, dosage, length of treatment and outcomes meaning we cannot say inositol is efficacious in all aspects of PCOS.(12)

Varying dosages and ratios are used in different studies. There is insufficient data to know which therapy (MI, DCI or a combined therapy) is most effective. Further research is required to understand long term safety and efficacy. There is insufficient data to support benefits in hirsutism, weight and pregnancy. Supplements can vary in quality. In the 2023 International Evidence-Based Guideline for PCOS it was suggested that ‘inositol can be considered an individual choice but there is insufficient evidence to make recommendations about which type, dosage or combination should be used’.(13)

6.2 Vitamin D

6.2.1 Introduction

Vitamin D is an important fat-soluble vitamin involved in calcium, phosphate and bone regulation. Plus, it has

a role in physiological processes. It can also help regulate insulin secretion, sensitivity and

inflammation. In recent years there has been lots of research looking into the effects of vitamin D deficiency in females with PCOS due to the links between vitamin D deficiency and insulin resistance.

Insulin resistance is a common complaint in PCOS patients, causing hyperinsulinaemia and impaired glucose metabolism. This can increase the risk of developing type 2 diabetes and cardiovascular disease. Research has shown that women with PCOS suffer with high prevalence of vitamin D deficiency.

6.2.2 Prevalence of Vitamin D deficiency in PCOS

Vitamin D deficiency is a common issue in women with PCOS. Low serum levels of 25-hydroxyvitamin D [25 (OH)D]. Research has shown that up to 70% of women with PCOS suffer with vitamin D deficiency (Kohlhoff et al., 2024). Due to the link between vitamin D deficiency and insulin resistance, vitamin D supplementation has been looked at as a nutritional intervention to improve metabolic profiles.

6.2.3 Mechanism of action of vitamin D in PCOS

Vitamin D can work in several ways to improve insulin secretion and sensitivity:

Calcium influx – Increasing calcium influx in pancreatic β-cells. Can help increase insulin secretion and production. Calcium is essential for pancreatic β-cell function.

Increased insulin sensitivity – Work on insulin signalling in skeletal muscle cells and adipose tissue. Aids regulation of insulin receptor substrate-1 (IRS-1).

Glucose regulation – Work on glucose transporter 4 (GLUT-4) in skeletal muscle cells. Can increase glucose uptake in muscle and adipose tissues. Vitamin D receptors – Binding to vitamin D receptors in the cell nucleus. Can have effects on calcium uptake and insulin related metabolic pathways.

6.2.4 Role of vitamin D in PCOS

Vitamin D supplementation has been looked at: Improved insulin resistance – Can improve insulin sensitivity by working on insulin signalling and pancreatic β-cells. Some research has shown that fasting insulin and HOMA-IR levels were decreased. Improved glucose regulation – Some research has shown that vitamin D can improve fasting glucose levels. Improved pancreatic β-cells – Can help regulate normal insulin secretion by working on calcium regulation in pancreatic β-cells. Improved metabolic disorders – Can help improve metabolic disorders by working on insulin secretion, glucose uptake and insulin sensitivity.

6.2.5 Clinical evidence of vitamin D supplementation in PCOS

A systematic review was carried out to look at the effect of vitamin D supplementation on insulin resistance and glycaemic control in women with PCOS (Kohlhoff et al., 2024). 9 studies were analysed with sample sizes between 28-180. Only 3 studies showed statistically significant improvements in fasting glucose. 2 studies showed improvements in fasting insulin and HOMA-IR. 5 studies showed no improvements. None of the studies showed any improvements in HbA1c. There were many reasons for the inconsistencies in the results. Different vitamin D supplement doses, duration of supplements, vitamin D levels and participant differences. Overall vitamin D supplementation can provide some metabolic benefits to some women with PCOS however the results were unclear.

6.2.6 Factors affecting vitamin D supplementation

There are many factors that can impact vitamin D supplementation in women with PCOS. Deficiency – If vitamin D deficient. Dosage and duration – Different vitamin D doses and duration. Body mass index (BMI) – Different body types. Genetics – Different vitamin D receptor gene polymorphism. Lifestyle – Sunlight exposure, diet, ethnicity and activity levels.

6.2.7 Limitations and safety Although vitamin D supplementation seems to provide some potential benefits there are uncertainties regarding its effectiveness. Many limitations were found during my research. There was a lack of appropriate clinical trials. Different methods of supplementation. Participant differences. Overall most studies didn't show any significant improvements in insulin resistance or glycaemic control. Therefore vitamin D shouldn't be used as a standalone treatment. Consideration should be given to the individuals

nutritional needs and if they are vitamin D deficient. Overuse can result in hypercalcaemia. Appropriate supplementation should be provided to ensure healthy vitamin D levels.

6.2.8 Conclusion

Vitamin D is an important nutrient that can help regulate metabolic disorders associated with PCOS. It can work on insulin secretion, sensitivity, calcium regulation and glucose metabolism. Clinical evidence has shown that some women with PCOS improved their fasting glucose, insulin and HOMA-IR however results were inconsistent. There is not enough evidence to suggest vitamin D supplementation would be an effective standalone treatment. Correction of vitamin D deficiencies should be considered as an adjunct in women with PCOS along with lifestyle and standard medical treatments. More well-designed clinical trials are needed to determine the long-term benefits of vitamin D.(14)

6.3 B complex vitamins

6.3.1 Introduction

B complex vitamins are a group of water soluble vitamins required for energy production, cellular metabolism and DNA. Vitamins B1 (Thiamine), B6 (Pyridoxine), B9 (Folate/Folic acid), and B12 (Cobalamin) are particularly important due to being involved in homocysteine metabolism and normal metabolic function. Polycystic Ovary Syndrome is often associated with insulin resistance, hormonal imbalance and metabolic issues. Women with PCOS may experience altered homocysteine metabolism which is linked to insulin resistance and cardiovascular risk. Inadequate consumption of certain B complex vitamins (particularly B12 and folate) may increase homocysteine levels.

This has led to research to investigate the use of B complex vitamin supplementation as a potential nutritional intervention for women with PCOS.

6.3.2 Mechanisms of Action in PCOS

The potential benefits of B complex vitamins in PCOS are mainly related to their role in regulating homocysteine metabolism and the methionine cycle.

1. Regulating homocysteine metabolism

Homocysteine is an amino acid created when methionine is metabolised. B complex vitamins (particularly B6, B9 and B12) are involved in converting and recycling homocysteine. Adequate levels of B complex vitamins can help regulate homocysteine levels.

2. Methionine cycle

B9 and B12 are involved in remethylation of homocysteine to methionine. B6 is also involved in the transsulphuration pathway to convert homocysteine to cysteine. This helps regulate homocysteine metabolism.

3. Regulating metabolic issues

Elevated homocysteine levels have been associated with insulin resistance and cardiovascular disease. Maintaining adequate levels of B vitamins can help regulate homocysteine levels and so improve cardiometabolic health.

4. Vitamin B12 and Metformin treatment

Metformin is commonly prescribed to treat insulin resistance in women with PCOS. It may affect the absorption of vitamin B12, especially in long term treatment. This can alter homocysteine metabolism. So it is important to ensure women taking metformin long term have adequate levels of B12.

6.3.3 Role in managing PCOS

Researchers have investigated whether B complex vitamins can be used to manage metabolic issues related to PCOS.

1. Regulate homocysteine levels – B6, B9 and B12 are all involved in homocysteine metabolism. Having adequate levels may help reduce high homocysteine levels which are associated with insulin resistance and cardiovascular risk.
2. Help with metabolic health – B complex vitamins are involved in metabolising carbohydrates, proteins and amino acids. They help regulate energy production and metabolism.
3. Reduce vitamin B12 deficiency caused by metformin – Long term use of metformin may reduce the absorption of B12. Supplementation may help

prevent or treat deficiency in vulnerable women with PCOS.

4. Improve oxidative stress markers – Some clinical studies have shown folate supplementation may have potential benefits on oxidative stress and inflammatory markers in women with PCOS.
5. Help with reproductive health – Folate and B12 are involved in DNA synthesis and cellular growth. Having adequate intakes are important for normal reproductive health and pre-conception. However there is no evidence to suggest B complex supplementation can improve fertility in women with PCOS.

6.3.4 Clinical Evidence

Alesi et al. (2022) investigated the current evidence for supplementing women with PCOS with B group vitamins and the relationship between homocysteine metabolism and metabolic issues.

One RCT was included in the review. Kilicdag et al. (2005) looked at 60 women with PCOS who were undergoing treatment with metformin. The participants were divided into 3 groups:

1. Metformin only.
2. Metformin and B group vitamins.
3. Metformin and folic acid.

After 12 weeks of treatment metformin alone increased homocysteine levels by 26.5%. However, supplementing with B group vitamins decreased homocysteine levels by 21.17% and folic acid decreased levels by 8.33%. There was no real improvement in insulin resistance (measured by HOMA-IR). This indicates that supplementing with B group vitamins may help counteract increased homocysteine levels caused by metformin treatment however, it is unclear if it will have an impact on insulin resistance.

6.3.5 Role of Folate (Vitamin B9)

Folate is an important B complex vitamin. Researchers have looked at using folate supplementation on its own in women with PCOS. Alesi et al. (2022) showed 2 RCTs were conducted to look at the effects of folate supplementation. Bahmani et al. (2014) and Asemi et al. (2014). The first study looked at 69 women with PCOS. They were given either 1mg/day, 5mg/day of folate or placebo over 8 weeks. The group receiving the highest dose had decreased levels of homocysteine, HOMA-β, hs-CRP and MDA. Levels of TAC and GSH were increased. Asemi et al. also looked at folate supplementation in 81 women with PCOS over 8 weeks. They found that supplementing with higher doses of folate resulted in decreased homocysteine, fasting blood insulin and HOMA-IR. Some lipid improvements were also noted. Overall it appears folate supplementation may help regulate homocysteine levels, reduce oxidative stress and improve some metabolic issues however more research is needed to confirm this.

6.3.6 Safety and Limitations

Generally B complex vitamins are well tolerated at appropriate levels. However over-supplementation can cause issues, particularly with vitamin B6 causing peripheral neuropathy when taken at high doses for long periods. There are several limitations to consider: There is currently limited clinical research looking at B complex vitamins and PCOS. Only one RCT has looked specifically at supplementing women with PCOS with combined B1, B6 and B12. Effects on insulin resistance are inconsistent. There is insufficient evidence showing improvements in reproductive health. Optimal dosage and period of supplementation is unknown. Supplementation should be tailored to individuals based on their nutritional requirements and deficiencies.

6.3.7 Conclusion

B complex vitamins (particularly B1, B6, B9 and B12) are essential for energy production, homocysteine regulation, DNA synthesis and normal cellular metabolism. Their involvement in the methionine cycle and homocysteine metabolism make them good candidates for investigation in relation to PCOS management. Clinical studies have shown that supplementing with B group vitamins may help reduce high homocysteine levels, particularly in women undergoing metformin treatment. Folate supplementation has also shown promising results on some metabolic and oxidative stress markers. However there is limited evidence and does not show consistent improvements in insulin resistance or reproductive health. Therefore they may act

as a beneficial nutritional component to help manage PCOS, particularly if the individual is deficient. More well-designed clinical trials are needed to confirm their effects.(15)

6.4 Omega-3 fatty acids

There are 3 different types of omega-3 fatty acids. These include; Alpha linolenic acid (ALA), Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA). ALA can be found in plant based sources such as; Flax seeds, chia seeds and walnuts. Whilst EPA and DHA can be found in fatty fish and fish oils. PCOS is linked to many metabolic disorders including insulin resistance, dyslipidaemia, chronic low-grade inflammation and hormonal imbalances. Omega-3 fatty acids have been shown to impact insulin, lipid and inflammatory regulation therefore this area of research has been of interest. Omega-3's have been studied as a nutritional intervention to aid with metabolic disorders.

6.4.1 Types of Omegas-3 And Function

There are 3 types of Omega-3 fatty acids. Alpha linolenic acid (ALA) Essential Omega-3 fatty acid. Found in plant based sources. Acts as a precursor to EPA and DHA but only in small amounts. Eicosapentaenoic acid (EPA) Long chain Omega-3 fatty acid. Found in marine based sources. Help produce lipid mediators to aid with inflammatory regulation. Docosahexaenoic acid (DHA) This is an important Omega-3 fatty acid. Long chain Omega-3 fatty acid found in fish and marine oils. This plays a key role in cellular membranes especially in the brain and retina. EPA and DHA are key omega-3 fatty acids and should be supplemented.

6.4.2 Mechanism of Action of Omega-3 Fatty Acids In PCOS

Omega-3 fatty acids can help improve metabolic disorders associated with PCOS by; Improving Insulin Sensitivity Impact mitochondrial and endoplasmic reticulum function. Insulin sensitivity in woman with PCOS can be improved by this Lipid Regulation Help to regulate triglyceride and cholesterol. Involved in lipid metabolism. Reduced Inflammation EPA and DHA help produce lipid mediators to help with inflammatory regulation. Supplementation will help reduce chronic low grade inflammation. Adiponectin Regulation Hormone produced by adipose tissue. Involved in glucose and lipid metabolism. Supplementation can help increase adiponectin levels in circulation. Can help improve insulin sensitivity. Oxidative Stress Regulation May help regulate pathways involved in oxidative stress and antioxidants. Can help regulate oxidative stress in those with metabolic disorders.

6.4.3 Role of Omega-3 Fatty Acids In PCOS

Omega-3 fatty acids can provide many benefits to help with metabolic disorders. Insulin Resistance – Supplementation can help improve insulin sensitivity and glucose metabolism via insulin pathways. Clinical trials have shown improvement in insulin and HOMA IR levels.

Improved Lipid Profile – Helps improve triglyceride levels. Improves total and LDL cholesterol. Reduced Waist Circumference – Some clinical trials showed reduction in waist circumference. Increased Adiponectin – Supplementation can help increase adiponectin in circulation. Linked to improved insulin sensitivity. Improved Glucose Metabolism – May help improve glucose metabolism. Improve fasting plasma glucose. Overall Omega-3 fatty acids may prove to be an effective supplement to help with metabolic disorders.

6.4.4 Clinical Evidence of Omega-3 Supplementation In PCOS

A Systematic Review and Meta-analysis conducted by Zhou et al (2023) looked at the effects of Omega-3 PUFA supplementation on metabolic profiles in women with PCOS. 11 randomised control trials were conducted with a total of 816 participants. Participants received Omega-3 supplements from marine based sources (Fish oil, EPA and DHA) and some from plant based sources (Flaxseed oil). Supplementation ranged from 8-24 weeks with doses ranging from 1000mg-4000mg per day. The meta-analysis showed; Improvement in Insulin Resistance – Improved insulin sensitivity, reduced fasting insulin and HOMA-IR. Improved Glucose – Improved blood glucose levels. Reduced fasting plasma glucose. Improved Lipid Profile – Improved lipid metabolism, reduced triglycerides, total and LDL cholesterol. Increased

Adiponectin – Increased adiponectin. Indicates improved metabolism. Reduced Waist Circumference – Reduced waist circumference. No improvements in body weight. Sub-analysis indicated improvements were greater in those taking supplements for longer than 8 weeks.

Omega-3 fatty acids may provide positive effects to improve insulin resistance and lipid metabolism in women with PCOS. Further clinical research is needed to confirm this.

6.4.5 Safety Issues and Limitations

Omega-3 fatty acids are generally well tolerated. However some may experience mild side effects such as nausea, fishy taste, indigestion and stomach issues.

Limitations: Different dosages. Different types. Small sample. No improvements in body weight, BMI, HDL cholesterol or hs-CRP. More research needs to be carried out to confirm Omega-3 is a safe and effective intervention for women with PCOS. It should be used as a supplementary nutritional intervention.

6.4.6 Conclusion

Omega-3 fatty acids are essential nutrients that have shown potential to aid with nutritional interventions in PCOS. They help regulate insulin pathways, lipid metabolism and inflammation. Clinical evidence shows Omega-3 fatty acid supplementation can help to improve insulin sensitivity, reduce triglycerides and cholesterol levels, increase adiponectin and improve metabolic health in women with PCOS. There were inconsistent results with body weight. Omega-3 fatty acids may provide some benefits and can be used as supplementary nutraceuticals. However, with appropriate dietary changes, exercise and medical intervention further large-scale clinical trials need to be carried out to determine what the optimum dose and duration of Omega-3 supplementation is to determine if it is an effective intervention to manage PCOS.(16)

6.5 N-Acetylcysteine (NAC)

6.5.1 N-Acetylcysteine (NAC) in the Treatment of Polycystic Ovary Syndrome (PCOS)

Review of antioxidant N-acetylcysteine in the treatment of polycystic ovary syndrome Pu Yifu (2024). This article is free and looks at the antioxidant properties of NAC.

N-Acetylcysteine (NAC) is an antioxidant drug derived from the amino acid L-cysteine. It is a precursor to glutathione, a vital intracellular antioxidant used to protect cells from oxidative damage. Recently, NAC has gained interest as a possible adjunctive nutraceutical to help with PCOS due to its antioxidant, anti-inflammatory and insulin sensitising properties. PCOS is associated with hormonal imbalances, insulin resistance and increased oxidative stress. This can cause issues with ovarian function, irregular menstrual cycles and issues with fertility. NAC has been looked at as a way to help improve these metabolic and fertility issues. However, the exact mechanisms of action and benefits are not fully understood. Biochemical Properties & Mechanisms of Action The main action of NAC is to provide the cysteine needed to produce glutathione. Glutathione is a vital antioxidant that helps destroy reactive oxygen species (ROS).

Increased oxidative stress is thought to contribute to PCOS. This can cause damage to the ovarian cells, insulin signalling and issues with fertility. NAC can help increase glutathione which reduces oxidative damage.

6.5.2 Mechanism of action:

Antioxidant: NAC can help increase glutathione within the cells.

This helps to reduce ROS and oxidants. This can help protect ovarian tissue. Anti-inflammatory: NAC can help reduce oxidative stress to help regulate the inflammatory process.

This can be beneficial as PCOS is associated with low grade chronic inflammation.

Anti-apoptotic: High oxidative stress can lead to increased apoptosis (programmed cell death) in ovarian cells. NAC can help reduce cell damage and abnormal apoptosis caused by oxidative stress. Improving insulin signalling: NAC can help change insulin signalling in insulin sensitive cells and pancreatic beta cells. This can help improve metabolic functioning related to insulin and reduce issues related to insulin resistance in PCOS.

6.5.3 Role of NAC in Managing PCOS

Clinical Evidence

Studies have been carried out looking at using NAC as a single intervention or with conventional medication to treat PCOS. Findings have shown that NAC can be beneficial in reducing oxidative stress, inflammation and changing insulin signalling. Some studies have looked at metabolic, ovarian and fertility issues. Results weren't consistent and may depend on the patient group, how long the patients were treated for and if they were taking other medications. The review by Pu (2024) looked at over 100 research articles. It highlighted that NAC has potential to help reduce oxidative stress and has anti-inflammatory and anti-apoptotic properties.

It also looked at how it can affect insulin target cell and pancreatic beta cell signalling pathways.

However, more research is needed to determine its clinical use in PCOS.

6.5.4 Safety & Limitations

NAC has been used in many therapeutic situations however is generally looked at as an adjunctive therapy. There is a need to know how safe and effective it is in women with PCOS long term.

There isn't clear evidence to determine a specific dose or how long to take NAC for PCOS.A major issue with research is that there is variation in the study designs, what NAC was used with and what clinical outcomes were looked at. Although NAC does have promising antioxidant and metabolic properties it shouldn't be used as an alternative to conventional PCOS treatments.

More well designed clinical trials are needed to determine the correct dose, long term safety and effects on fertility and metabolic outcomes.

6.5.5 Conclusion

N-Acetylcysteine is a promising antioxidant nutraceutical that can help manage PCOS. This is because it increases glutathione levels and has antioxidant, anti-inflammatory and anti-apoptotic properties.Due to its potential to affect insulin signalling and ovarian cell functioning it is a promising area of research in nutrition and therapeutics. Initial findings suggest it may have benefits for reducing oxidative stress however more clinical studies are needed to determine how effective, safe and useful it can be as a therapeutic in women with PC.(17)

7. Mechanisms of Action

7.1 Mechanism of antioxidants

Antioxidants have mostly protective roles in the diet by improving the endogenous antioxidant mechanism. Polyphenols induce Nrf2 pathway, stimulate antioxidant enzymes such as SOD, CAT, GPx and GST and modulate inflammatory pathways to reduce oxidative stress.(18)

7.2 Mechanism of action of anti-inflammatory in PCOS.

Metformin improves insulin sensitivity by decreasing hepatic glucose production, gut glucose absorption and circulating insulin. By inhibiting mitochondrial complex I, metformin will activate AMPK to improve glucose uptake and lipid metabolism. This helps reduce hyperinsulinemia and lipotoxicity which can help to restore normal ovulation and menstrual cycle patterns in women with PCOS.(19)

7.3 Flavonoids in Modulating Polycystic Ovary Syndrome (PCOS) Pathways

Flavonoids (e.g. quercetin, naringenin, luteolin and EGCG) can help manage PCOS as they are able to improve insulin sensitivity via increasing AMPK activity and insulin signalling pathways, reducing oxidative stress and inflammation, improving pancreatic β-cell function and reducing hyperinsulinemia. This then reduces insulin stimulated ovarian androgen production. Studies have shown that flavonoids can improve insulin sensitivity and hormonal balance, plus reduce fasting insulin and HOMA-IR levels. However, due to poor bioavailability and fast metabolism these compounds have limited efficacy. Flavonoids therefore have potential as nutraceuticals to manage PCOS but would require further clinical studies to determine their therapeutic benefits.(20)

8. Clinical Evidence and Research Findings

8.1 Introduction

Clinical Evidence on Nutraceuticals in Pcos Includes Randomized Controlled Trials (rcts), Systematic Reviews, Meta-analyses, And Network Meta-analyses. These Studies Assess Supplements As Adjuncts To Standard Care, Often Through Metabolic, Hormonal, Reproductive, And Inflammatory Outcomes. Results Differ By Supplement, Formulation, Population, And Outcome. Changes In Laboratory Markers Should Not Automatically Be Interpreted as Improved Fertility, Symptom Control, Or Long-term Health.

8.2 RANDOMIZED CONTROLLED TRIALS

RCT Have Evaluated Inositol, Vitamin D, Omega-3, Probiotics, Chromium, Carnitine, Coq10, And Combinations. Trial Findings Vary Because Doses, Duration, Baseline Nutrient Status, Diagnostic Criteria, And Co-interventions Are Not Uniform. Small Trials May Detect Changes In Insulin Or Lipid Markers But Are Often Underpowered To Assess Pregnancy, Live Birth, Long-term Complications, Or Uncommon Harms. A Guideline-informing Review Of Inositol Included 30 Trials With 2,230 Participants; 19 Trials Contributed To Meta-analyses. It Found Possible Benefits For Some Metabolic Measures And A Potential Ovulatory Benefit For D-chiro-inositol, But Effects Were Not Consistent Across All Outcomes. Metformin May Improve Some Outcomes More, While Inositol May Cause Fewer Gastrointestinal Adverse Effects.(10)

8.3 SYSTEMATIC REVIEWS AND META-ANALYSES

A 2022 Umbrella Review Reported Favorable Effects for Some Metabolic Outcomes with Inositol, Vitamin D, Probiotics/synbiotics, Omega-3, And Curcumin. It Also Found Evidence That Inositol May Increase Ovulation In Subfertile Women With Pcos. Certainty Varied By Outcome, And High-certainty Evidence For Improved Health Or Reproductive Outcomes Was Lacking. [2] A 2025 Network Meta-analysis Pooled 79 Rcts Involving 5,501 Participants And Compared 30 Supplement Interventions Or Combinations. It Reported Differences Across Selected Lipid, Insulin-resistance, Antioxidant, And Hormonal Markers. No Significant Supplement-placebo Differences Were Found For Several Hormones And Inflammatory Markers, Including Total Testosterone, Shbg, Dheas, And Hs-crp. [3] Meta-analysis Cannot Eliminate Weaknesses In Original Trials. Inconsistent Formulations and Outcomes Can Make Pooled Estimates Less Applicable to Individual Patients.(21)

8.4 COMPARATIVE EFFECTIVENESS

Network Meta-analysis Combines Direct Comparisons with Indirect Comparisons Through a Shared Comparator. A 2023 Review Of 41 Articles And 2,362 Participants Reported That Carnitine, Inositol, And Probiotics Were Associated With Lower Body Weight Or Bmi Versus Placebo; Omega-3 And Chromium Showed Favorable Findings For Selected Glucose-metabolism Measures; And Coq10 Ranked Favorably For Some Lipid Outcomes. The Authors Cautioned That Publication Bias And The Need For Better Rcts Limited Confidence. [4] Rankings Should Not Be Treated As A Definitive “best Supplement” List. A High Rank May Rely On Indirect Evidence, Sparse Comparisons, Or Uncertain Estimates. Comparative Results Apply to The Outcome Measured—not Necessarily to Symptoms, Fertility, Safety, Or Overall Pcos Management.(22)

8.5 CLINICAL OUTCOMES

Outcomes Include Metabolic Measures (fasting Insulin, Homa-ir, Glucose, Lipids), Hormones (testosterone, Shbg, Lh), Reproductive Endpoints (cycle Regularity, Ovulation, Pregnancy, Live Birth), Symptoms, And Patient-reported Quality of Life. Many Trials Emphasize Surrogate Laboratory Outcomes Rather Than Outcomes Patients Directly Experience. A 2026 Systematic Review And Meta-analysis Of 78 Studies Reported Pooled Reductions In Fasting Insulin And Lh And An Increase In Shbg, While Findings For Ovarian Follicle Count And Menstrual Bleeding Were Inconsistent. Interpretation Was Limited by Heterogeneity and Variable Study Quality.(23)

8.6 INTERPRETATION AND LIMITATIONS

Evidence Requires Caution Because Pcos Definitions and Participant Characteristics Differ; Formulations and Doses Are Not Standardized; Studies May Be

Small or Short; Combinations Complicate Attribution; Adverse Events Are Incompletely Reported; And Surrogate Endpoints May Not Predict Meaningful Benefit. Network Rankings Depend On Whether Included Trials Are Sufficiently Comparable. Current Evidence Supports Further Study Of Selected Nutraceuticals As Adjuncts, Not Replacements For Evidence-based Pcos Care. Decisions Should Consider the Clinical Goal, Pregnancy Plans, Medicines, Possible Interactions, Product Quality, And Clinician Advice.

8.7 CONCLUSION

Some Nutraceuticals May Improve Selected Metabolic or Hormonal Measures in Pcos, And Inositol May Have a Role in Selected Reproductive Outcomes. Comparative Superiority And Durable Patient-important Benefit Remain Uncertain. Future Trials Need Standardized Products, Clear Diagnostic Criteria, Adequate Sample Sizes, Longer Follow-up, And Consistent Reporting of Adverse Effects, Pregnancy Outcomes, And Quality of Life. (23)

9. COMBINATION NUTRACEUTICAL THERAPY

9.1 Myo-inositol and D-chiro-inositol

Biological roles and rationale. Myo-inositol (MI) and D-chiro-inositol (DCI) are stereoisomers of inositol involved in insulin-related intracellular signalling. MI participates in pathways associated with glucose uptake and follicle-stimulating hormone signalling, while DCI participates in insulin-mediated metabolic processes, including glycogen synthesis. Altered insulin signalling and ovarian function in PCOS provide a rationale for studying them together. These mechanisms are plausible, but do not by themselves establish clinical benefit. The combination is intended to address complementary roles. MI is commonly studied for reproductive and ovarian outcomes, while DCI is studied for metabolic outcomes. Response may vary with PCOS phenotype, baseline insulin resistance, formulation, dose, and duration. A proposed “physiological” MI:DCI ratio is often discussed, but the ideal ratio and dose have not been established for everyone with PCOS.

Clinical evidence and limitations. Trials and reviews report possible improvements in selected outcomes, such as menstrual regularity, ovulatory function, insulin-related measures, or androgen-related markers. Studies differ in dose, ratio, duration, comparators, and outcome definitions; some are small or have methodological limitations. Evidence is insufficient to identify one formulation as universally superior or to replace established PCOS care.

Safety and practical considerations: Inositol’s are generally well tolerated in studies; gastrointestinal symptoms are among the more commonly reported adverse effects. Product quality and ingredient amounts vary. People using glucose-lowering medicines, undergoing fertility treatment, pregnant, or managing other conditions should discuss supplementation with a qualified clinician. Supplements are not a substitute for individualized medical assessment.(24)

9.2 Vitamin and mineral combinations

Vitamin D. Vitamin D supports calcium balance and has roles in metabolic and reproductive physiology. Low vitamin D status is frequently reported in PCOS populations, but association does not prove supplementation treats PCOS. Studies of vitamin D alone or in combinations report mixed effects on insulin-related, lipid, inflammatory, or reproductive outcomes. Correcting a documented deficiency may be appropriate; high-dose use without clinical guidance is not.

Vitamin B12 and folate. Folate and B12 are required for DNA synthesis and normal red-blood-cell formation. They may be relevant when dietary intake is inadequate or when a person uses metformin, which can be associated with lower B12 levels in some patients. Folate is also important before and during early pregnancy. These nutrients address nutritional needs; they are not established stand-alone PCOS treatments. Consider diet, medicines, laboratory results, and pregnancy plans.

Minerals: zinc and magnesium. Zinc contributes to enzyme function and normal reproductive physiology; magnesium participates in glucose metabolism and many enzymatic reactions. Studies have explored these minerals in PCOS, sometimes alongside vitamins or inositols, but findings are inconsistent and do not

establish a standard combination. Excess intake can be harmful: prolonged high-dose zinc can impair copper status; supplemental magnesium can cause gastrointestinal effects and may be risky with impaired kidney function. Combination approach. Multinutrient products may combine vitamin D, B vitamins, folate, zinc, magnesium, or other ingredients. They can be convenient when correcting multiple documented deficiencies, but more ingredients do not automatically mean greater efficacy. Doses, interactions, duplicate ingredients across products, and nutritional status matter. Evidence for a multi-ingredient product cannot identify which ingredient caused an observed effect.(25)

Synergistic effects: Meaning of synergy. Synergy means the combined effect of two or more components is greater than expected from their separate effects under a defined comparison. A combination producing a benefit is not, by itself, proof of synergy: the effect may be additive, driven mainly by one component, or due to correcting a deficiency. Proposed synergy in PCOS. MI and DCI may act through overlapping but non-identical insulin-signalling pathways, providing a rationale for studying them together. Vitamins and minerals support normal enzymatic, metabolic, or reproductive functions, particularly when a deficiency exists. These are plausible rationales, not proof that a specific mixture improves PCOS outcomes more than its ingredients separately.Strong evidence would require comparative trials including the combination and each component alone, appropriate doses, prespecified meaningful outcomes, and a test of whether the combined effect exceeds the expected additive effect. Trials should report adverse events and account for baseline nutrient status, diet, medication use, and PCOS phenotype. Many studies lack these comparisons, so synergy claims warrant caution.(26)

10. SAFETY, DOSAGE AND LIMITATION

10.1 EARLIER SYSTEMATIC REVIEW: SAFETY LIMITATIONS

Arentz Et Al. (2017) Included 24 Randomized Studies Involving 1,406 Women and Examined Seven Nutritional Supplements and Four Herbal Medicines. Only Seven Studies (164 Participants) Investigated Adverse Effects. No Included Study Was Judged To Have Low Risk Of Bias. The Review Found Insufficient High-quality Evidence For Menstrual Regulation And Concluded That Evidence About Safety Was Lacking. This Is a Crucial Caution: Absence of Reported Harm Is Not Proof of Absence of Harm, Particularly When Follow-up Is Short and Adverse Events Are Not Systematically Collected.(26)

10.2 INOSITOL: FORMS AND EVIDENCE

Myo-inositol (mi) And D-chiro-inositol (dci) Are Insulin-signaling-related Compounds. Trials Use Different Doses, Ratios, Durations, And Co-ingredients, So Results Cannot Be Generalized Across Products. The 40:1 Mi:dci Ratio Is Frequently Studied, But An Optimal Formulation Is Not Firmly Established For Every Pcos Phenotype Or Outcome. Potential Benefits Reported In Trials Include Insulin-related Markers, Ovulatory Function, And Menstrual Regularity; Certainty Varies. Discuss Use with A Clinician, Especially If Taking Glucose-lowering Medication or Trying to Conceive.(27)

10.3 INOSITOL: ADVERSE EFFECTS AND INTERACTIONS

Reported Tolerability Is Often Good, But Possible Effects Include Gastrointestinal Discomfort, Nausea, Diarrhea, Headache, Dizziness, Or Fatigue. Long-term Safety And Product-specific Interaction Data Are Limited. A Theoretical/clinically Relevant Concern Is Additive Glucose Lowering With Insulin, Metformin, Or Other Glucose-lowering Agents; Monitor Symptoms And Clinician-directed Glucose Measurements When Applicable. Do Not Assume That A “natural” Product Is Interaction-free. Pregnancy And Fertility Treatment Require Clinician Review of Formulation and Dose.(27)

VITAMIN D

Vitamin D Is Often Studied Because Deficiency May Coexist with Pcos and Because Vitamin D Participates in Calcium, Bone, And Metabolic Physiology. Supplementation Is Most Defensible When Deficiency Or Inadequate Intake Is Identified; Pcos-specific Benefits Remain Variable. Studies Use Different Baseline Levels And Doses, Making Pooled Conclusions Difficult. Consider 25-hydroxyvitamin D Testing When

Clinically Indicated Rather Than Taking High Doses Empirically.

VITAMIN D: SAFETY AND INTERACTIONS

Excess Vitamin D Can Cause Hypercalcemia and Hypercalciuria, With Nausea, Constipation, Weakness, Confusion, Kidney Stones, Or Kidney Injury in Severe Cases. Risk Rises With Excessive Dosing And Certain Conditions. Thiazide Diuretics Can Increase Hypercalcemia Risk; Orlistat And Bile-acid Sequestrants May Reduce Absorption; Corticosteroids Can Affect Vitamin D/calcium Metabolism. Digoxin Users Need Special Caution Because Hypercalcemia May Increase Arrhythmia Risk. High-dose Regimens Should Be Clinician-supervised.(27)

OMEGA-3 FATTY ACIDS

Omega-3 (EPA/DHA)

Clinical investigations have explored the utility of omega-3 supplementation in patients with polycystic ovary syndrome (PCOS) to ameliorate elevated triglyceride levels, attenuate inflammatory markers, and optimize cardiometabolic profiles.Despite these potential benefits, the ingestion of omega-3s is frequently associated with adverse gastrointestinal manifestations, including nausea, acid reflux, and general digestive distress.Furthermore, administration at high doses may precipitate an increased risk of hemorrhage, a concern that is markedly amplified when concomitant therapy involves anticoagulants or antiplatelet agents.

N-acetylcysteine (NAC)

The administration of N-acetylcysteine (NAC) has been investigated for its potential to ameliorate metabolic derangements in patients with polycystic ovary syndrome (PCOS). However, therapeutic use may be complicated by gastrointestinal adverse events, including nausea, vomiting, diarrhea, and general digestive distress.Furthermore, NAC exhibits a clinically significant interaction with nitroglycerin, which can precipitate severe headaches and hypotension; consequently, concurrent medication regimens require careful evaluation and vigilant monitoring.

Probiotics/Synbiotics: Research into probiotic and synbiotic supplements for patients with polycystic ovary syndrome (PCOS) has demonstrated their potential to ameliorate markers of inflammation, insulin resistance, lipid profiles, and androgen excess; however, therapeutic efficacy is contingent upon the specific bacterial strains and formulation employed. While these agents offer clinical promise, they may precipitate gastrointestinal adverse events such as bloating, flatulence, and general digestive distress.-Consequently, individuals with compromised immune function must exercise heightened caution when considering such interventions. Coenzyme Q10/Vitamin E: Investigations into antioxidants such as Coenzyme Q10 and vitamin E have focused on their potential to ameliorate oxidative stress alongside metabolic and reproductive markers.

While certain studies indicate favorable shifts in these specific biomarkers, the existence of tangible clinical benefits remains equivocal.Coenzyme Q10 carries a risk of precipitating gastrointestinal disturbances and necessitates caution regarding interactions with warfarin, whereas vitamin E administration may elevate the propensity for hemorrhage.

Chromium and Other Minerals: Research has explored chromium's capacity to augment insulin sensitivity and optimize metabolic markers, although it is important to note that other minerals, including selenium, zinc, magnesium, and calcium, have demonstrated efficacy in improving these same indicators.Consequently, the supplementation of these trace elements should ideally be restricted to instances where a confirmed deficiency exists.It is equally critical to recognize that excessive chromium consumption can precipitate renal or hepatic complications, while an overdose of selenium may manifest as alopecia, nail dystrophy, and gastrointestinal disturbances.

Herbals: While an extensive array of herbs—including cinnamon, berberine, spearmint, resveratrol, and curcumin—has been scrutinized for their potential to optimize metabolic parameters and androgenic profiles, the empirical support for their efficacy remains scant.

This limitation stems primarily from the paucity of data, which is further compromised by small sample sizes and brief intervention durations.Clinically, significant safety concerns accompany their use: berberine is associated with gastrointestinal distress and possesses the capacity to interact with a wide spectrum of

pharmacological agents.Similarly, excessive consumption of cinnamon may precipitate hepatic complications due to coumarin content, whereas resveratrol and curcumin carry risks of coagulopathy and adverse drug interactions. Pregnancy/Fertility The advisability of these measures may vary contingent upon one's reproductive status, specifically regarding pregnancy, lactation, or the administration of fertility therapies.

Currently, the evidentiary base remains inadequate to ascertain the safety of numerous such interventions during gestation.Individuals suffering from renal or hepatic pathologies, diabetes, thyroid disorders, coagulopathies, or immune deficiencies must exercise prudence.Furthermore, the consumption of herbal preparations and high-dose vitamin supplements during pregnancy is contraindicated absent explicit authorization from a qualified medical practitioner. (10,24,28)

11. FUTURE PERSPECTIVE

11.1 Research gap: inconsistent study designs

Primary studies differ in diagnostic criteria, inclusion and exclusion criteria, baseline nutrient status, PCOS phenotype, body mass index, diet, supplement dose, intervention length, comparator, and outcome measurement. These differences can create substantial heterogeneity and limit pooled analyses. Some studies use multi-ingredient products, making it difficult to identify which component contributes to an observed effect. Future trials should follow the current international PCOS diagnostic guideline, clearly define phenotype and baseline characteristics, and report a complete intervention description. Protocols should identify primary and secondary outcomes before recruitment. Consistent methods will improve reproducibility, reduce selective reporting, and make future systematic reviews more reliable.(21,26,29)

11.2 Future randomized controlled trials

Large, multicenter randomized controlled trials are needed to establish efficacy and safety. Trials should be adequately powered, use appropriate placebo or active comparators, and include diverse participants. Sample-size calculations should be based on clinically meaningful differences rather than convenience. Investigators should publish protocol registration, allocation methods, blinding, adherence, withdrawals, and all prespecified outcomes. Follow-up should be long enough to evaluate sustained effects and delayed adverse events. A short trial may detect a change in insulin or lipid markers but cannot establish long-term reproductive, cardiovascular, or pregnancy safety. Replication across independent research groups is essential before a nutraceutical is recommended broadly.(21)

Standardization of nutraceutical products : Product standardization is a major priority. Publications should identify the exact ingredient, chemical form, dose, source, ratio, formulation, manufacturer, batch number, purity, and quality testing. Researchers should report whether the product was independently tested for identity, contaminants, adulterants, and label accuracy. Without these details, results cannot be reproduced and consumers cannot know whether commercial products match the trial intervention. For multi-ingredient formulations, investigators should consider factorial or component designs that distinguish the contribution of each ingredient. A combination that appears beneficial does not establish that every component is necessary. Standardization will strengthen evidence synthesis, enable dose-response evaluation, and support responsible regulation.(15,21)

11.3 Safety, adverse events, and pharmacovigilance

Safety: It is important to report the safety profile of the interventions with information on severity, duration and outcome. Only 41.2% of studies reported adverse effects.

Drug-Nutraceutical Interactions: Many patients with PCOS take supplements alongside drugs, including metformin, hormonal contraception, thyroid meds and fertility drugs, therefore it should be considered in studies. Monitoring medications and working with pharmacists can help reduce any risk.

Personalised Treatment: PCOS has a high degree of variability in terms of reproductive and metabolic characteristics. Future studies should focus on examining how effective nutraceuticals may be depending on PCOS phenotype, BMI, insulin resistance, age, nutrition deficiency and fertility goals. This could help

identify which supplements would be suitable to use and provide safe and personalised treatment options. protocols. (15,21,26)

11.4 Guidelines and translation into practice

The 2023 international PCOS guideline emphasizes evidence-based care, shared decision-making, lifestyle support, emotional wellbeing, and recognition of broader metabolic and reproductive risks. Nutraceutical evidence should be integrated only when sufficiently reliable and clinically relevant. Future guidelines should identify specific indications, evidence certainty, safety considerations, and monitoring rather than recommending supplements generically. Implementation research should examine how clinicians discuss supplements, how patients obtain products, and what barriers affect adherence. Patient education should explain uncertainty, interactions, pregnancy considerations, and product quality. Supplements should not delay evaluation or replace treatments with established benefits. Shared decision-making should account for patient values, affordability, and treatment burden.(15,29)

11.5 Conclusion and key future priorities

The future of nutraceutical research in PCOS depends on high-quality evidence rather than the number of supplements studied. Current reviews highlight promising signals but also substantial heterogeneity, limited psychological outcomes, and incomplete adverse-event reporting. Research must standardize diagnosis, interventions, dose, duration, and outcome definitions while ensuring adequate sample size and follow-up. The highest priorities are: well-designed multicenter trials; product and dose standardization; long-term safety and interaction monitoring; phenotype-specific and deficiency-targeted research; patient-important reproductive and psychological outcomes; real-world surveillance; and transparent systematic reviews. The most useful future result will be clear evidence about which supplement, for whom, for what outcome, at what dose, and with what safety profile.

REFERENCES

1. Forslund M, Melin J, Stener-Victorin E, Hirschberg AL, Teede H, Vanky E, et al. International evidence-based guideline on assessment and management of <scp>PCOS</scp> —A Nordic perspective. Acta Obstet Gynecol Scand. 2024;103 (1):7–12. DOI: 10.1111/aogs.14725
2. Farhana AA, Shi J. A Narrative Review on Global Epidemiology of PCOS and its Hormonal Management. SSR Institute of International Journal of Life Sciences. 2024;10 (3):5516–21. DOI: 10.21276/SSR-IIJLS.2024.10.3.17
3. Harada M. Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. Reprod Med Biol. 2022;21 (1). DOI: 10.1002/rmb2.12487
4. Kalra EK. Nutraceutical-definition and introduction. AAPS PharmSci. 2003;5 (3):27–8. DOI: 10.1208/ps050325
5. Dong J, Rees DA. Polycystic ovary syndrome: pathophysiology and therapeutic opportunities. BMJ Medicine. 2023;2 (1):e000548. DOI: 10.1136/bmjmed-2023-000548
6. Mancini A, Bruno C, Vergani E, d'Abate C, Giacchi E, Silvestrini A. Oxidative Stress and Low-Grade Inflammation in Polycystic Ovary Syndrome: Controversies and New Insights. Int J Mol Sci. 2021;22 (4):1667. DOI: 10.3390/ijms22041667
7. González F. Inflammation in Polycystic Ovary Syndrome: Underpinning of insulin resistance and ovarian dysfunction. Steroids. 2012;77 (4):300–5. DOI: 10.1016/j.steroids.2011.12.003
8. Kalra B, Kalra S, Sharma J. The inositols and polycystic ovary syndrome. Indian J Endocrinol Metab. 2016;20 (5):720. DOI: 10.4103/2230-8210.189231
9. Dinicola S, Chiu TTY, Unfer V, Carlomagno G, Bizzarri M. The rationale of the myo-inositol and D-chiro-inositol combined treatment for polycystic ovary syndrome. The Journal of Clinical Pharmacology. 2014;54 (10):1079–92. DOI: 10.1002/jcph.362
10. Fitz V, Graca S, Mahalingaiah S, Liu J, Lai L, Butt A, et al. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 Update of the International Evidence-

based PCOS Guidelines. J Clin Endocrinol Metab. 2024;109 (6):1630–55. DOI: 10.1210/clinem/dgad762

11. The 40:1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: comparison with other ratios.
12. Fitz V, Graca S, Mahalingaiah S, Liu J, Lai L, Butt A, et al. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 Update of the International Evidence-based PCOS Guidelines. J Clin Endocrinol Metab. 2024;109 (6):1630–55. DOI: 10.1210/clinem/dgad762
13. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Human Reproduction. 2023;38 (9):1655–79. DOI: 10.1093/humrep/dead156
14. Kohlhoff G, Kirwan R, Mushtaq S. The effect of vitamin D supplementation on markers of insulin resistance in women with polycystic ovarian syndrome: a systematic review. Vol. 63, European Journal of Nutrition Springer Science and Business Media Deutschland GmbH; 2024. p. 2859–69.
15. Alesi S, Ee C, Moran LJ, Rao V, Mousa A. Nutritional Supplements and Complementary Therapies in Polycystic Ovary Syndrome. Advances in Nutrition. 2022;13 (4):1243–66. DOI: 10.1093/advances/nmab141
16. Zhou J, Zuo W, Tan Y, Wang X, Zhu M, Zhang H. Effects of n-3 polyunsaturated fatty acid on metabolic status in women with polycystic ovary syndrome: a meta-analysis of randomized controlled trials. Vol. 16, Journal of Ovarian Research BioMed Central Ltd; 2023.
17. Yifu P. A review of antioxidant N-acetylcysteine in addressing polycystic ovary syndrome. Gynecological Endocrinology. 2024;40 (1). DOI: 10.1080/09513590.2024.2381498
18. Hunyadi A. The mechanism (s) of action of antioxidants: From scavenging reactive oxygen/nitrogen species to redox signaling and the generation of bioactive secondary metabolites. Med Res Rev. 2019;39 (6):2505–33. DOI: 10.1002/med.21592
19. Attia GM, Almouteri MM, Alnakhli FT. Role of Metformin in Polycystic Ovary Syndrome (PCOS): Related Infertility. Cureus. 2023; DOI: 10.7759/cureus.44493
20. Dutta S, Sengupta P, Rao S, Elgarawany GE, Samrot AV, Rosas IM, et al. Targeting Polycystic Ovary Syndrome (PCOS) Pathophysiology with Flavonoids: From Adipokine–Cytokine Crosstalk to Insulin Resistance and Reproductive Dysfunctions. Pharmaceuticals. 2025;18 (10):1575. DOI: 10.3390/ph18101575
21. Zhao G, Fan Y, Li R, Huang Y, Li W, Zhao Y, et al. The effectiveness of nutritional supplements in improving polycystic ovary syndrome in women: a systematic review and network meta-analysis. Reproductive Biology and Endocrinology. 2025;23 (1):94. DOI: 10.1186/s12958-025-01409-9
22. Hu X, Wang W, Su X, Peng H, Tan Z, Li Y, et al. Comparison of nutritional supplements in improving glycolipid metabolism and endocrine function in polycystic ovary syndrome: a systematic review and network meta-analysis. PeerJ. 2023;11:e16410. DOI: 10.7717/peerj.16410
23. Çelik ZM, Kurnaz D, Özcan A, Keskin E, Sayın Ünlügedik E, Aktaç Ş. The effect of nutraceutical interventions on reproductive health outcomes in women with polycystic ovary syndrome: A systematic review and meta-analysis. Diabetes Obes Metab. 2026;28 (2):1213–33. DOI: 10.1111/dom.70307
24. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2023;108 (10):2447–69. DOI: 10.1210/clinem/dgad463
25. Zhang J, Xing C, Zhao H, He B. The effectiveness of coenzyme Q10, vitamin E, inositols, and vitamin D in improving the endocrine and metabolic profiles in women with polycystic ovary

syndrome: a network Meta-analysis. Gynecological Endocrinology. 2021;37 (12):1063–71. DOI: 10.1080/09513590.2021.1926975

26. Menichini D, Ughetti C, Monari F, Di Vinci PL, Neri I, Facchinetti F. Nutraceuticals and polycystic ovary syndrome: a systematic review of the literature. Gynecological Endocrinology. 2022;38 (8):623–31. DOI: 10.1080/09513590.2022.2089106
27. Arentz S, Smith CA, Abbott J, Bensoussan A. Nutritional supplements and herbal medicines for women with polycystic ovary syndrome; a systematic review and meta-analysis. BMC Complement Altern Med. 2017;17 (1):500. DOI: 10.1186/s12906-017-2011-x
28. Kachhawa G, Senthil Kumar K V., Kulshrestha V, Khadgawat R, Mahey R, Bhatla N. Efficacy of myo-inositol and <scp>d</scp> -chiro-inositol combination on menstrual cycle regulation and improving insulin resistance in young women with polycystic ovary syndrome: A randomized open -label study. International Journal of Gynecology & Obstetrics. 2022;158 (2):278–84. DOI: 10.1002/ijgo.13971
29. Scannell N, Mantzioris E, Rao V, Pandey C, Ee C, Mousa A, et al. Type and Frequency in Use of Nutraceutical and Micronutrient Supplementation for the Management of Polycystic Ovary Syndrome: A Systematic Scoping Review. Biomedicines. 2023;11 (12):3349. DOI: 10.3390/biomedicines11123349

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