THORNE

PCOS Professional Product Guide

Companion to the PCOS Support Guide

Welcome to the PCOS Professional Product Guide companion to the **PCOS Support Guide**. While the Support Guide is to be shared with your patients, we know that practitioners often want more information – to dig deeper into the research that supports our choice of ingredients. This Product Guide is intended to give you that deeper dive. It is written for practitioners only so please don't distribute it to your patients/clients.

You will find a page at the back of the patients' PCOS Support Guide to "write in" your individualized prescription – diet, supplements, and lifestyle recommendations. It can be printed out or written on electronically for ease of emailing to patients.

It is our hope that this product information will help guide you in your choice of supplements.

Metabolic support formulas

A significant number of women with PCOS also have metabolic syndrome (MetS; 47 percent according to one study) or components of it. Having a high BMI is one of the most significant contributing factors. And because both MetS and PCOS share insulin resistance/hyperinsulinemia as an etiological factor, treatment of PCOS should include a metabolic focus (glucose/insulin, lipids, weight/body composition, fatty liver, etc.).

Metabolic Health

Thorne's **Metabolic Health** combines two highly-absorbable botanical-phospholipid complexes – bergamot phytosome (Vazguard®) and curcumin phytosome (Meriva®) – for lipid, glucose, fatty liver, weight management, and metabolic syndrome support.

Meriva and/or Vazguard for aspects of cardiometabolic/liver health are supported by at least 14 clinical trials. The following is a sampling.

/ Bergamot polyphenolic fractions (BPF)/BPF phytosome (Vazguard)

According to the **CDC**, more than half the women with PCOS who are overweight will develop type 2 diabetes by age 40.

Bergamot phytosome improves cardiometabolic markers in type 2 diabetes and demonstrates superior bioavailability.

In a double-blind, placebo-controlled trial, 60 patients with type 2 diabetes and dyslipidemia were randomized to one of three groups: (1) 650 mg twice daily of bergamot polyphenol fractions (BPF; 1,300 mg BPF daily), (2) 500 mg twice daily of bergamot phytosome (40% bergamot; containing 400 mg BPF daily), or (3) placebo for 30 days. Standard biomarkers for cardiometabolic disease were measured at baseline and after 30 days, including total cholesterol, LDL, HDL, triglycerides (TGs), fasting glucose, and lipoprotein particle size and number.

Significant decreases of LDL and total cholesterol, TGs, and fasting blood sugar were found in both bergamot groups compared to placebo after 30 days, *with equivalent results between the BPF and BPF-phytosome group* – albeit with significantly lower bergamot doses in the phytosome group (400 mg in the phytosome group versus 1,300 mg in the non-phytosome group). The bergamot groups also had decreased numbers of small, dense LDL particles in favor of larger, less dense particles.

Mollace V, Scicchitano M, Paone S, et al. Hypoglycemic and hypolipemic effects of a new lecithin formulation of bergamot polyphenolic fraction: a double blind, randomized, placebo- controlled study. *Endocr Metab Immune Disord Drug Targets.* 2019;19(2):136-143. doi: 10.2174/1871530319666181203151513.

Metabolic Health

Bergamot phytosome lowers cholesterol and decreases visceral fat in overweight adults.

In a randomized, double-blind, placebo-controlled trial, 64 sedentary overweight or obese subjects (ages 18-60) with mild hypercholesterolemia received either 500 mg bergamot (as BPF) phytosome twice daily or placebo for 12 weeks. Blood chemistry and body composition were tested at baseline and at 30, 60, and 90 days.

There was a statistically significant decrease in visceral adipose tissue (VAT) in the bergamot group after 12 weeks compared to baseline, with no such decrease in the placebo group. The bergamot group also had a statistically significant decrease in LDL and total cholesterol compared to baseline. Compared to the placebo group, the bergamot group had statistically significantly lower LDL and VAT.

Rondanelli M, Peroni G, Riva A, et al. Bergamot phytosome improved visceral fat and plasma lipid profiles in overweight and obese class I subject with mild hypercholesterolemia: A randomized placebo controlled trial. *Phytother Res* 2021 Apr;35(4):2045-2056. doi: 10.1002/ptr.6950.

NAFLD is common in women with PCOS.

According to one study, 23.8 percent of the women with PCOS had non-alcoholic fatty liver disease (NAFLD) compared to 3 percent in the control group. Thus, fatty liver is something to consider with PCOS patients.

Romanowski MD, Parolin MB, Freitas AC, et al. Prevalence of non-alcoholic fatty liver disease in women with polycystic ovary syndrome and its correlation with metabolic syndrome. *Arq Gastroenterol.* 2015;52(2):117-123.

BPF improves cardiometabolic markers in subjects with NAFLD and metabolic syndrome.

In a randomized study, 107 patients received 650 mg of bergamot polyphenolic fractions (BPF) or placebo twice daily for 120 days. Inclusion criteria included NAFLD diagnosed on ultrasound and concurrent MetS, diagnosed by having at least three of five MetS criteria (elevated blood sugar, increased waist circumference, high triglycerides, high blood pressure, and low HDL cholesterol).

Fasting blood samples, collected at the beginning and end of the 4-month study, were tested for total cholesterol, LDL, HDL, TGs, fasting blood sugar, and liver enzymes. Lipoprotein particle size and number, C-reactive protein (CRP), and TNF-α were also measured.

Statistically and clinically significant decreases in fasting blood sugar, total cholesterol, LDL, TGs, liver enzymes, and inflammatory biomarkers CRP and TNF-α, and increased HDL cholesterol were observed in the bergamot group after four months compared to baseline levels. Subjects taking BPF also experienced decreased fatty infiltration of the liver on ultrasound. BPF also improved lipid particle size and number ratios – with significant decreases in small, dense, atherogenic LDL particles and an increase in large, less dense particle size and number.

Gliozzi M, Carresi C, Musolino V, et al. The effect of bergamot-derived polyphenolic fraction on LDL small dense particles and non alcoholic fatty liver disease in patients with metabolic syndrome. *Adv Biol Chem* 2014;4(2): DOI: 10.4236/abc.2014.42017

BPF improves lipid profiles and lowers fasting blood sugar while benefiting statin-sensitive individuals without side effects.

In a double-blind, placebo-controlled trial, 237 subjects with (1) high cholesterol, (2) high cholesterol + high TGs, or (3) high cholesterol, TGs, and fasting blood sugar were given 500 or 1,000 mg BPF or placebo once daily, before eating, for 30 days. Another group of statin-intolerant individuals, after a 2-month washout, were given 1,500 mg BPF daily.

Both doses of bergamot polyphenolic fractions resulted in significant decreases in total cholesterol and LDL (with concomitant increases in HDL), TGs, and fasting blood sugar, with the most dramatic decreases in the group with all three (high cholesterol, TGs, and blood sugar); no such changes were seen in the placebo groups. In statin-intolerant individuals, 1,500 mg BPF for 30 days resulted in an average 27-percent reduction in LDL without the side effects they experienced with a statin.

Mollace V, Sacco I, Janda E, et al. Hypolipemic and hypoglycaemic activity of bergamot polyphenols: from animal models to human studies. *Fitoterapia* 2011;82(3):309-316.

⁄ Curcumin phytosome (Meriva)

Like bergamot, curcumin is a poorly absorbed flavonoid compound. Curcumin bound to phospholipids as a phytosome significantly increases absorption by as much as 29 times.

Curcumin phytosome decreased LDL cholesterol, triglycerides, and uric acid in patients with NAFLD.

In an 8-week, controlled trial, 87 NAFLD patients were randomized to receive 500 mg curcumin phytosome (as Meriva) twice daily or a placebo; all received the same dietary guidance. Blood levels of lipids, glucose, and uric acid were tested before and at the end of the trial; anthropometric measurements – weight and BMI – were also taken.

At the end of eight weeks, subjects in the curcumin group had significantly lower total cholesterol, LDL, TGs, and uric acid (all except uric acid were significantly higher in the curcumin group than the control group at baseline). There were no significant changes in fasting blood sugar or HDL levels. Lipid levels (except TGs) and uric acid were higher in the control group at the end of the study than at baseline, with no changes in TGs or HDL throughout the study.

Panahi Y, Kianpour P, Mohtashami R, et al. Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: A randomized controlled trial. *J Cardiovasc Pharmacol* 2016;68(3):223-229.

Curcumin phytosome decreased liver enzymes and fat accumulation in NAFLD.

In a double-blind, placebo-controlled trial, 87 NAFLD patients were randomized to receive 500 mg curcumin phytosome as Meriva (n=44) or placebo (n=43) twice daily for eight weeks. Anthropometric measurements, liver enzymes, and liver ultrasound were performed at baseline and the end of the study.

Supplementation resulted in significant decreases in liver enzymes (AST and ALT) in the Meriva group; whereas, the placebo group had significant increases in liver enzymes. On ultrasound, 75 percent of the curcumin group showed improvement in liver fat accumulation, compared to 4.7 percent in the placebo group. Anthropometric measurements of BMI and waist circumference were significantly decreased in the Meriva group compared to the placebo group.

Panahi Y, Kianpour P, Mohtashami R, et al. Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: a randomized controlled trial. *Drug Res* (Stuttg) 2017 Apr;67(4):244-251. doi: 10.1055/s-0043-100019.

Curcumin phytosome (Meriva) and/or omega-3s improve insulin sensitivity and lipids in prediabetes.

In a randomized, controlled trial, 81 participants with prediabetes were randomly assigned to: (1) double placebo, (2) 500 mg curcumin phytosome + placebo twice daily, (3) 1,000 mg fish oil + placebo twice daily, or (4) 500 mg curcumin phytosome + 1,000 mg fish oil twice daily; supplements were taken with morning and evening meals. Primary endpoints were changes in blood sugar indices – fasting blood sugar, HbA1c, serum insulin, and HOMA-IR; secondary outcomes were serum lipid levels.

The curcumin-only group had significant improvements in insulin resistance from baseline, whereas the other groups did not. There were no differences in fasting glucose, HbA1c, or anthropometric measurements among the groups or compared to baseline. Regarding secondary outcomes, TGs were significantly decreased in all treatment-active groups compared to placebo, although the magnitude of the change was greatest in the fish oil-only group.

Thota R, Acharya S, Garg M. Curcumin and/or omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance and blood lipids in individuals with high risk of type 2 diabetes: a randomised controlled trial. *Lipids Health Dis* 2019;18(1):31.

Curcumin phytosome (Meriva) and/or fish oil for blood sugar metabolism

In a crossover study, 16 healthy volunteers were randomly assigned to one of four treatments, then switched to the others in random order with one washout week in between. The protocol was curcumin phytosome (two tablets containing 90 mg curcumin each) + two placebo capsules, two fish oil capsules (1.2 grams of omega-3s total) + two placebo tablets, same amounts of curcumin + fish oil, or double placebo, all in one dose prior to eating a somewhat high-carb, high-fat breakfast.

Metabolic Health

Blood levels of glucose, triglycerides, and insulin were tested at time 0, then at 60 and 120 minutes post-meal.

Postprandial glucose at 60 minutes was significantly lower in the curcumin (60.6%), curcumin + fish oil (51%), and fish oil-only (30%) groups compared to the placebo group. Area under the curve for glucose concentrations were similarly reduced in the curcumin (36%) and curcumin + fish oil (30%) groups. Area under the curve changes for serum insulin were significantly lower for curcumin (26.5%) and fish oil + curcumin (25.8%) groups, but decreases were non-statistically significant (18%) in the fish oil-only group – all compared to placebo.

Thota R, Dias C, Abbott K, et al. Curcumin alleviates postprandial glycaemic response in healthy subjects: A cross-over, randomized controlled study. *Sci Rep* 2018;8(1):13679. doi: 10.1038/s41598-018-32032-x.

Along with increased waist circumference, low HDL cholesterol is one of the most prevalent metabolic syndrome factors experienced by women with PCOS.

Low-dose curcumin phytosome (Meriva) improved leptin:adiponectin ratios and increased HDL in NAFLD patients.

A low dose of 250 mg curcumin phytosome once daily or placebo was studied in an 8-week, double-blind trial of 65 NAFLD patients. Lipid profiles, liver enzymes, leptin, adiponectin, fasting blood sugar, and anthropometric measurements were taken at the beginning and end of the study.

After eight weeks, subjects in the Meriva group had significantly lower leptin and increased adiponectin, a decreased leptin:adiponectin ratio, and increased HDL cholesterol compared to placebo.

NOTE: Leptin at high levels is a sign of leptin resistance – that it is not telling the brain it's time to stop eating. Adiponectin stimulates fatty acid oxidation and glucose uptake in the cells. In obese people, leptin levels tend to be high and adiponectin levels low.

Mirhafez S, Farimani A, Dehhabe M, et al. Effect of phytosomal curcumin on circulating levels of adiponectin and leptin in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. *J Gastrointestin Liver Dis* 2019 Jun 1;28:183-189. doi: 10.15403/jgld-179.

/ Green tea phytosome

Green Tea Phytosome contains 250 mg of green tea/phospholipid complex per capsule. Green tea as a phytosome has 3-times better absorption than unbound green tea.

Green tea phytosome improves metabolic syndrome status.

Fifty individuals with borderline metabolic syndrome took 150 mg green tea phytosome (GTP) twice daily for 24 weeks along with diet and lifestyle changes; they were compared to 50 borderline MetS subjects who engaged in diet and lifestyle changes only (control group). By the end of the study, 68 percent of those in the GTP group compared to 20 percent in the control group had improved, so they no longer were considered to be borderline MetS. Improvements were seen in the GTP group in waist circumference (in women), body weight, fasting glucose, HDL cholesterol, and blood pressure.

Belcaro G, Ledda A, Hu S, et al. Greenselect phytosome for borderline metabolic syndrome. *Evid Based Complement Alternat Med.* 2013;2013:869061. doi: 10.1155/2013/869061.

Green tea phytosome reduces weight and BMI.

In a similarly designed study, 50 overweight individuals took 150 mg GTP twice daily plus a low-calorie diet, while another 50 subjects did a low-calorie diet alone – both groups for 90 days. The group taking the GTP lost considerably more weight (14 kg versus 5 kg) and had significantly improved BMI compared to the diet-only group.

Di Pierro F, Menghi AB, Barreca A, et al. Greenselect Phytosome as an adjunct to a low-calorie diet for treatment of obesity: a clinical trial. *Altern Med Rev.* 2009;14(2):154-160.

Green tea phytosome helps maintain weight loss in overweight women.

In a study of 40 overweight women (average BMI 36), all underwent a 3-month lifestyle intervention that resulted in weight loss. For another three months they were randomly assigned to 150 mg GTP twice daily or placebo. After three months, those in the GTP group had continued to lose weight while there was an increase in the placebo group.

Gilardini L, Pasqualinotto L, Di Pierro F, et al. Effects of Greenselect Phytosome® on weight maintenance after weight loss in obese women: a randomized placebo-controlled study. *BMC Complement Altern Med.* 2016;16:233. doi: 10.1186/s12906-016-1214-x.

Green tea phytosome decreased visceral fat and improved metabolic markers in overweight women

In a randomized, placebo-controlled trial, 28 overweight postmenopausal women were assigned to 150 mg of GreenSelect Phytosome (GSP) or placebo twice daily before lunch and dinner for 60 days. Blood parameters, anthropometric measurements, and body composition were evaluated at baseline, 30 days, and 60 days. Both groups participated in a low-calorie diet.

The GSP group had a significant reduction in respiratory quotient – a reflection of fat and carbohydrate oxidation. Other findings in the GSP group included significant reductions in inflammatory markers (CRP and visceral adipose tissue), improved insulin sensitivity (HOMA-IR), decreased fat mass, and increased adiponectin and adiponectin-to-leptin ratio.

Rondanelli M, Gasparri C, Perna S, et al. A 60-day green tea extract supplementation counteracts the dysfunction of adipose tissue in overweight post-menopausal and Class I obese women. Nutrients. 2022;14(24):5209.

FiberMend®

⁄ Partially hydrolyzed guar gum

FiberMend contains Sunfiber®, a partially hydrolyzed guar gum (PHGG) fiber. Hydrolysis aids in solubility, decreases viscosity, and improves digestibility. Fiber is an essential component of a program for maintenance of healthy blood sugar and lipid levels by increasing satiety, slowing gastric emptying, and improving the metabolic profile of the gut microbiome.

PHGG reduces the glycemic index of foods.

Sunfiber can help reduce the glycemic index (GI) of the food with which it is consumed, which can, in turn, reduce post-prandial blood sugar and insulin. For example, the GI of white rice in healthy volunteers was 87.5 but decreased to 67.5 with 3 g of PHGG and 65.5 with 5 g. Similar decreases were seen in diabetics and with the addition of PHGG to white bread.

Trinidad T, Perez E, Loyola A, et al. Glycemic index of Sunfiber (Cyamoposis tetragonolobus) products in normal and diabetic subjects. *Int J Food Sci Technol* 2004;39:1093-1098.

PHGG improves cholesterol and glucose in young women.

Young women (n=15) with borderline or elevated total cholesterol (190 mg/dL or higher) were given 5 g or 15 g partially hydrolyzed guar gum daily for two weeks. The women in the higher PHGG group had significantly lower total cholesterol and fasting blood sugar at the end of two weeks, while the women in the 5-mg group experienced a trend toward improvement.

Yamatoya K, Kuwano K, Suzuki J. Effects of hydrolyzed guar gum on cholesterol and glucose in humans. *Food Hydrocolloids* 1997;11:239-242.

Berberine (Dual-Action Formula)

⁄ Berberine Phytosome (Berbevis® / Berberine HCl)

Many studies have demonstrated berberine can benefit metabolic derangements associated with PCOS, including specifically in women with PCOS. It also benefits some of the hormonal imbalances associated with PCOS. Thorne's **Berberine** dual-action formula contains 550 mg of berberine phytosome and 450 mg of berberine HCl in each 2-capsule serving.

Berberine phytosome shows 10-times better absorption than unbound berberine

Berberine phytosome is a berberine extract bound to phospholipids for enhanced absorption. A pK study found 10-times better absorption with the phytosome compared to unbound berberine.

Petrangolini G, Corti F, Ronchi M, et al. Development of an innovative berberine food-grade formulation with an ameliorated absorption: in vitro evidence confirmed by healthy human volunteer pharmacokinetic study. Evid Based Complement Alternat Med 2021;2021:7563889. doi: 10.1155/2021/7563889.

Berberine phytosome improves several biomarkers of PCOS

In a small pilot study, 12 normal-to-overweight women (average age 26) diagnosed with PCOS were given 550 mg berberine phytosome twice daily for 60 days. Numerous blood biomarkers, acne assessments, and a DEXA scan for body composition were conducted at the beginning of the study and after 60 days of supplementation. A statistically significant decrease in insulin resistance (measured by HOMA-IR), fasting blood sugar, inflammation (assessed by CRP and TNF-α), triglycerides, testosterone, BMI, visceral adipose tissue, fat mass, and acne assessed by two acne grading scales, along with a statistically significant increase in sex hormone-binding globulin, were observed after 60 days of supplementation.

Rondanelli M, Riva A, Petrangolini G, et al. Berberine phospholipid is an effective insulin sensitizer and improves metabolic and hormonal disorders in women with polycystic ovary syndrome: a one-group pretest-post-test explanatory study. Nutrients 2021;13(10):3665. doi: 10.3390/nu13103665.

Berberine improves hormone and metabolic abnormalities of PCOS.

In a meta-analysis of 12 different RCTs in PCOS, in terms of fertility berberine was shown to significantly decrease total testosterone and the ratio of LH to FSH compared to placebo but did not increase number of live births compared to placebo or metformin. In terms of metabolic markers, berberine decreased total cholesterol, waist circumference, and waist-to hip ratio compared to placebo and to metformin.

Xie L, Zhang D, Ma H, et al. The effect of berberine on reproduction and metabolism in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized control trials. *Evid Based Complement Alternat Med.* 2019;2019:7918631. doi: 10.1155/2019/7918631.

Berberine versus myo-inositol versus metformin for lipid, glucose, and hormone support in PCOS.

In an RCT, 129 women with PCOS were assigned to one of three groups: (1) 500 mg berberine HCl twice daily, (2) 1,000 mg myo-inositol twice daily, or (3) 500 mg metformin HCl twice daily for three months.

At the end of the trial, **lipid parameters** were improved in all three groups but more significantly in the berberine group compared to the other two groups: decreased total- and LDL-cholesterol and triglycerides and increased HDL. Regarding **hormone changes,** improvements were seen in all three groups: decreased total testosterone and free androgen index and increased SHBG. Improvement in SHBG and free androgen index were more significant in the berberine group. And regarding glucose regulation, improvements were seen in all three groups: decreased fasting glucose and fasting insulin and increased glucose-to-insulin ratio (a measure of insulin sensitivity). However, the group taking myo-inositol had significantly greater decreases in fasting insulin and increases in fasting glucose-to-insulin ratio – representing greater benefit for insulin resistance.

Thus, berberine was superior for sex hormone and lipid balance, while myo-inositol was superior for improving insulin sensitivity.

Mishra N, Verma R, Jadaun P. Study on the effect of berberine, myoinositol, and metformin in women with polycystic ovary syndrome: a prospective randomised study. *Cureus.* 2022;14(1):e21781. doi: 10.7759/cureus.21781.

Menstrual regularity/ fertility support

Ovarian Care

Ovarian Care offers a unique blend of nutrients and botanical extracts for your patients who need nutritional support for menstrual irregularity, fertility, and PCOS-related issues. Ovarian Care helps balance sex hormones, improves insulin sensitivity and blood sugar levels, and provides mitochondrial and antioxidant support.

/ Inositol: Myo-inositol and D-chiro-inositol

The importance of insulin and blood sugar metabolism in the etiology of PCOS is illustrated by a plethora of research on myo- and d-chiro-inositol in PCOS. Both forms of inositol play key roles in insulin signaling in the body – contributing to improved insulin sensitivity and blood sugar balance – and subsequent improvements in various aspects of PCOS. Studies have been conducted on each, as well as in combination. Ovarian Care contains the ideal ratio of myo- to d-chiro-inositol.

40 to 1: The ideal ratio of myo-inositol to D-chiro-inositol

While it is known that a combination of myo-inositol (MI) and D-chiro-inositol (DCI) provides benefit for women with PCOS, this study evaluated which combination provided the most beneficial ratio for improving the condition. Women with PCOS (n=56) were supplemented with 2 grams of inositol twice daily for three months. In terms of ratios, the women were divided into seven groups of eight each and supplemented with DCI alone or a ratio of MI-to-DCI of: 1:3.5, 2.5:1, 5:1, 20:1, 40:1, or 80:1. The primary outcome was restoration of ovulation, with secondary outcomes reflected in normalization of abnormal hormonal levels, including testosterone, progesterone, estradiol, and insulin. BMI, SHBG, and restoration of menses were also assessed.

The 40:1 ratio was the most effective at restoring ovulation, menses, and normalization of sex hormones (lowering testosterone and increasing progesterone and estradiol). Every formula was effective at improving insulin sensitivity. The researchers noted that DCI in higher amounts appeared to interfere with the benefits.

Nordio M, Basciani S, Camajani E. The 40:1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: comparison with other ratios. *Eur Rev Med Pharmacol* Sci 2019;23(12):5512-5521.

/ Myo-inositol with folate

Two studies have examined the effect of myo-inositol plus folate for improving reproductive outcomes. Ovarian Care contains 5-MTHF – folate in its active, tissue-ready form.

Myo-inositol and folate improve pregnancy rates in infertile women.

In an open-label, observational study, 3,602 infertile women were supplemented with 2 g myo-inositol and 200 mcg folate twice daily for 2-3 months. Primary outcomes were restoration of ovulation and pregnancy rates. Hormonal levels (testosterone, free testosterone, and progesterone) were tested in a subgroup of 32 women before and at the end of 12 weeks.

Seventy percent of the women experienced restored ovulation, which was reflected in 545 pregnancies (a pregnancy rate of 15.1%). In the subgroup who were hormone tested, testosterone decreased from an average of 96.6 ng/mL to 43.3 ng/mL, while progesterone increased from 2.1 ng/mL to 12.3 ng/mL. Better fertilization rates in a subgroup of women who underwent *in vitro* fertilization (IVF) were also noted.

Regidor PA, Schindler AE, Lesoine B, Druckman R. Management of women with PCOS using myo-inositol and folic acid. New clinical data and review of the literature. *Horm Mol Biol Clin Investig* 2018;34(2):/j/hmbci.2018.34.issue-2/hmbci-2017-0067/hmbci-2017-0067.xml.

Myo-inositol and folate improve fertilization rates in assisted reproduction.

A second double-blind trial examined the effect of 4 g MI plus 400 mcg folate (n=30) compared to 400 mcg folate only (n=30) in a group of poor ovarian responders to assisted reproduction. Interventions were provided for 12 weeks. Outcomes measured were number and quality of oocytes retrieved, amount of gonadotropin necessary to obtain each oocyte (ovarian sensitivity index), fertilization rate, and pregnancy rate.

The ovarian sensitivity index and fertilization rate were significantly higher in the group taking both MI and folate. Although the number of oocytes retrieved and pregnancy rates were both higher in the MI plus folate group, the differences between groups were not statistically significant.

Mohammadi S, Eini F, Bazarganipour F, et al. The effect of myo-inositol on fertility rates in poor ovarian responder in women undergoing assisted reproductive technique: a randomized clinical trial. *Reprod Biol Endocrinol* 2021;19(1):61.

/ Folate

It is particularly important to have a sufficient folate level prior to conception. Not only does folate help prevent neural tube birth defects during the first trimester of fetal development, but evidence also suggests a higher folate level improves the likelihood of becoming pregnant. The folate in Ovarian Care is provided as methylfolate (5-MTHF) for enhanced utilization in the body, including those individuals with challenged folate metabolism.

Higher folate levels increase pregnancy rates.

In one study, the women with the highest folate levels had more than a one-and-a-half times greater likelihood of becoming pregnant compared to women with the lowest folate levels.

Gaskins AJ, Chiu YH, Williams P, et al. Association between serum folate and vitamin B-12 and outcomes of assisted reproductive technologies. *Am J Clin Nutr* 2015;102(4):943-950.

Folate supplementation increased pregnancy rates.

In a study of 3,895 Danish women, those who reported taking folic acid alone or in a multivitamin had higher rates of pregnancy than women who did not take folic acid. Supplementation increased pregnancy rates by 10 percent in women with a regular menstrual cycle and by 36 percent in women with an irregular cycle.

Cueto HT, Riis AH, Hatch EE, et al. Folic acid supplementation and fecundability: a Danish prospective cohort study. *Eur J Clin Nutr* 2016;70(1):66-71.

⁄ CoQ10 phytosome (Ubiqsome®)

Coenzyme Q10 (CoQ10) provides nutrient support for the mitochondria and protects against oxidative damage to support healthy oocytes. Ovarian Care provides CoQ10 as a phytosome (Ubiqsome®; CoQ10 complexed with phospholipids) for enhanced absorption. One study of a single dose to heathy volunteers found three-times greater plasma levels compared to CoQ10 that was not complexed.

Supplementation increases follicular fluid levels of CoQ10.

For a supplement to provide benefit, it needs to get to the target tissue. In a small study, 15 women undergoing IVF were supplemented with 100 mg CoQ10 twice daily for 30 days prior to an IVF procedure and compared to a group of women undergoing IVF but not supplemented with CoQ10.

CoQ10 supplementation significantly increased follicular fluid CoQ10 levels compared to non-supplemented levels. In addition, follicular fluid total antioxidant capacity was lower in the supplemented group, indicating fewer free radicals in the fluid.

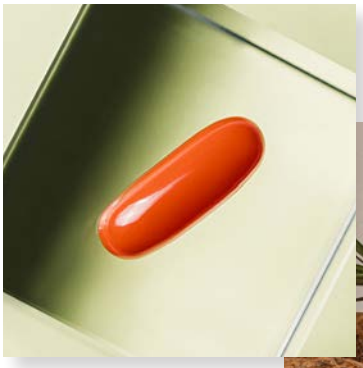
Giannubilo SR, Orlando P, Silvestri S, et al. CoQ10 supplementation in patients undergoing IVF-ET: the relationship with follicular fluid content and oocyte maturity. *Antioxidants* (Basel) 2018;7(10):141.

CoQ10 improves ovarian response to stimulation.

A primary reason for failure of assisted reproduction techniques is poor ovarian response (POV) to gonadotropin stimulation. Based on the theory that oxidative stress is one mechanism involved, a randomized, controlled trial was conducted with 169 women under age 35 with POV who were awaiting IVF treatment. For 60 days prior to their IVF procedure, women (n=76) were supplemented with 200 mg CoQ10 three times daily and compared to women (n=93) who were not supplemented. Outcomes measured included ovarian response and embryo quality.

Significant positive differences were found in the CoQ10-supplemented women, including: (1) lower gonadotropin stimulation requirements, (2) higher peak estradiol levels, (3) higher fertilization rate (67.5% versus 45% in controls), (4) more high-quality embryos, and (5) fewer procedure cancellations because of poor embryo development (8 versus 23). Overall, CoQ10 pretreatment resulted in improved ovarian response and embryo quality.

Xu Y, Nisenblat V, Lu C, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol* 2018;16(1):29.



N-acetylcysteine (NAC)

There have been a significant number of studies of NAC for various aspects of fertility. NAC, as a precursor to glutathione, has potent antioxidant and liver-supportive effects. Women with PCOS have a tendency toward increased inflammation and decreased antioxidant capacity, both of which can interfere with healthy oocyte production and ovulation. Thorne offers **NAC** in 500-mg capsules.

A meta-analysis shows NAC improves several hormone imbalances related to PCOS.

A meta-analysis assessed the results of 18 clinical trials on the use of NAC in 2,185 women with PCOS. Previous studies show improved ovulation and fertility rates using NAC as an adjunct to other treatments.

The meta-analysis found NAC significantly impacted hormones related to PCOS:

- **Testosterone.** NAC significantly decreased testosterone – more so in studies that were of at least eight weeks duration.
- **Follicle stimulating hormone (FSH):** NAC significantly increased FSH.
- **Estradiol.** In analyzing all studies, NAC did not impact estradiol levels, which, like testosterone, can be elevated in women who have PCOS. However, studies that combined NAC with metformin found it contributed to lower estradiol levels. Also, studies that used higher doses of NAC – 1.8 g/day significantly lowered estradiol, compared to studies that used 1.2 g/day.

Shahveghar Asl Z, Parastouei K, Eskandari E. The effects of N-acetylcysteine on ovulation and sex hormones profile in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Br J Nutr* 2023 Jan 4:1-9. doi: 10.1017/S0007114522003270.

Prevent or correct a deficiency

Women's Daily Probiotic

Women who have PCOS tend to have specific microbiome compositions. Their vaginal microbiomes tend to be characterized by a low number of *Lactobacillus* species, while their gut microbiomes tend to be characterized by reduced species diversity and lower numbers of beneficial short-chain fatty acids (for more information see **PCOS Support Guide**, Relationship Between the Microbiome and PCOS).

Thorne's **Women's Daily Probiotic** is a comprehensive blend that includes two highly studied proprietary probiotic blends along with two single *Lactobacillus* strains. This Thorne exclusive is designed specifically to support the needs of women. The eight strains of *Lactobacillus spp* include those most commonly found in a healthy vagina. In addition to improving vaginal flora, *Lactobacillus* strains in Women's Daily Probiotic have been shown to improve cardiometabolic risk factors in women.

L. plantarum improves fasting blood sugar and homocysteine.

In a 90-day study of 24 postmenopausal women with metabolic syndrome, half were given fermented milk with *L. plantarum* while the other half were given non-fermented milk. Women in the *L. plantarum* group showed a significant decrease in homocysteine levels and fasting glucose.

Barreto FM, Colado Simão AN, Morimoto HK, et al. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition* 2014;30(7-8):939-42. doi: 10.1016/j.nut.2013.12.004.

L. acidophilus improves cholesterol.

A meta-analysis of 11 studies on the effects of probiotics for lowering lipids found significant lowering of total- and LDL-cholesterol with probiotics – *L. acidophilus* in particular. This is an especially intriguing benefit, because elevated cholesterol is commonly seen in women with PCOS.

Shimizu M, Hashiguchi M, Shiga T, et al. Meta-analysis: effects of probiotic supplementation on lipid profiles in normal to mildly hypercholesterolemic individuals. *PLoS One* 2015;10(10):e0139795. doi: 10.1371/journal.pone.0139795.

Vitamin D-5,000

Women with PCOS, particularly if they are contending with weight issues, tend to have low vitamin D levels, which can contribute to insulin resistance and hormone imbalances. Supplementing with vitamin D, particularly at a moderate dose might provide the most benefit for improving several of the metabolic derangements in PCOS. Thorne offers vitamin D in several strengths, including D-5,000 with 5,000 IU vitamin D per capsule.

Vitamin D (4,000 IU) decreased total testosterone and improved other hormonal imbalances in PCOS.

In a study of women with PCOS, daily vitamin D intake helped improve several metabolic derangements. In a RCT 90 insulin-resistant women with PCOS (n=30 per group) were given 1,000 IU vitamin D3, 4,000 IU vitamin D3, or placebo for 12 weeks. Significant decreases in total testosterone, free androgen index, hs-CRP, and hirsutism and increases in SHBG and total antioxidant capacity were seen in the 4,000 IU group compared to 1,000 IU or placebo.

Jamilian M, Foroozanfard F, Rahmani E, et al. Effect of two different doses of vitamin D supplementation on metabolic profiles of insulin-resistant patients with polycystic ovary syndrome. *Nutrients*. 2017;9(12):1280. doi: 10.3390/nu9121280.

Vitamin D decreased testosterone and ADMA in PCOS.

In another study 50,000 IU of D3 were given to women with PCOS and low vitamin D status once a week for eight weeks, followed by maintenance doses of 880 IU vitamin D and 1,000 mg calcium (from 2,500 mg calcium carbonate). This protocol led to significant decreases in total testosterone and asymmetric dimethylarginine (ADMA) and increases in SHBG. Decreased ADMA results in improvement in endothelial function.

Sert ZS, Yılmaz SA, Seçilmiş Ö, et al. Effect of calcium and vitamin D supplementation on the clinical, hormonal, and metabolic profile in non-obese women with polycystic ovary syndrome. *Ir J Med Sci.* 2022 Dec;191(6):2657-2662. doi: 10.1007/s11845-021-02899-3.

Vitamin D improved hormone status, menstrual regularity, and follicle number.

In a study of overweight women with PCOS, 30 were assigned to 50,000 IU D3 weekly and 30 to placebo for 12 weeks. The women in the vitamin D group had decreased testosterone and hirsutism, increased SHBG and menstrual regularity, and improved follicle number and ovarian size on ultrasound.

Al-Bayyari N, Al-Domi H, Zayed F, et al. Androgens and hirsutism score of overweight women with polycystic ovary syndrome improved after vitamin D treatment: A randomized placebo controlled clinical trial. *Clin Nutr.* 2021;40(3):870-878. doi: 10.1016/j.clnu.2020.09.024.

Super EPA

The omega-3 fatty acids EPA and DHA are essential components of a protocol for PCOS. They have been shown to improve insulin sensitivity and decrease triglycerides and inflammation.

Supplementing omega-3 fatty acids might provide more benefit than D alone.

Sixty women with PCOS were randomized to 50,000 IU vitamin D every two weeks and 2,000 mg/day omega-3 fish oil or placebo for 12 weeks. At the end of the study, women taking vitamin D plus omega-3s experienced decreased testosterone, hs-CRP, and malondialdehyde (sign of oxidative stress), along with increased antioxidant capacity and improved depression and anxiety scores.

Jamilian M, Samimi M, Mirhosseini N, et al. The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome. *J Affect Disord.* 2018 Oct 1;238:32-38. doi: 10.1016/j.jad.2018.05.027.

***EPA and DHA** improved several aspects of PCOS.*

In an RCT, 64 overweight or obese women with PCOS were given 720 mg EPA and 480 mg DHA or placebo daily for eight weeks. Those in the omega-3 group had significant increases in adiponectin and decreased glucose, insulin resistance, and total- and LDL-cholesterol compared to placebo; while they also had decreased triglycerides and increased HDL compared to baseline.

Mohammadi E, Rafraf M, Farzadi L, et al. Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome. *Asia Pac J Clin Nutr.* 2012;21(4):511-518.

EPA and DHA lower triglycerides in metabolic syndrome.

A review of randomized controlled trials found that daily administration of greater than one gram per day of EPA and DHA to metabolic syndrome patients for at least three months allowed for a significant reduction (7-25%) in triglycerides. Lowering triglycerides can reduce inflammation and atherogenic small density LDL as well.

Lopez-Huertas E. The effect of EPA and DHA on metabolic syndrome patients: a systematic review of randomised controlled trials. *Br J Nutr* 2012;107 Suppl 2:S185-SI94.

5-MTHF

According to one study 70 percent of women with PCOS have insufficient dietary intake of folate – which is especially concerning if a woman is trying to become pregnant. (See more on folate and PCOS in Ovarian Care above). Thorne offers folate in its tissue-ready form as 5-MTHF in 1-mg and 5-mg capsules.

In addition to sharing the PCOS Support Guide with your patients, we also offer you a Fertility Guide to share with your patients.

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800-228-1966 | support@thorne.com | thorne.com

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