Oocyte SAP

*Science-based female fertility support**

Female infertility is a contributing factor for about one third of infertility cases. The cause of female infertility is linked to ovulation problems and damage to fallopian tubes, which indicates lack of health of the reproductive system in general. These symptoms are mainly reflected in the quality and number of oocytes, which are diminished in an impaired reproductive system. The oocyte has the highest number of mitochondria and mitochondrial DNA copies of any cell. The status and function of mitochondria is crucial to oocyte quality, fertilization of oocyte, and embryo development. Poor oocyte quality in one of the leading causes of failed in vitro fertilization (IVF).* Other fertilization techniques such as intrauterine insemination (IUI) are also heavily dependent on ovulation cycles and oocyte quality. Disorders in reproductive system are also characterized by further complications such as polycystic ovary disease (PCOS), accompanied by hyperandrogenism, insulin resistance, abnormal lipid profile and oxidative stress.* Oocyte health impacts reproductive and overall health beyond fertility.* Previous treatments for infertility and PCOS with clomiphene citrate and gonadotropins are not without their own complications, and a natural and safe alternative is required to improve oocyte quality and reproductive health.*

Oocyte SAP is a synergistic formulation of key evidence based nutraceuticals that can help improve egg quality in patients trying to conceive, undergoing fertility treatment, or with PCOS.* By supporting cell health and improving mitochondrial function and oocyte micro-environment, **Oocyte SAP** aims at improving overall reproductive health.* Ingredients in this unique formulation can help reduce oocyte mitochondrial DNA damage, attenuate oxidative stress and improve insulin sensitivity and blood lipid profiles, thereby providing a wholesome therapeutic approach to enhance reproductive health.* NFH also offers **Male Fertility SAP**, a cofactor science based formula designed to support sperm production and longevity.*

SUPPLEMENT FACTS

Serving Size: 2 Capsules
Servings Per Container: 60

	Amount Per Serving	% Daily Value
Vitamin C	100 mg	111%
Vitamin E (as D-*alpha*-tocopherol)	5 mg AT	55%
myo-Inositol	500 mg	**
Acetyl-L-carnitine hydrochloride	250 mg	**
N-Acetyl-L-cysteine	250 mg	**
PQ_{10} (emulsified coenzyme Q_{10})	100 mg	**
R–alpha-Lipoic acid	100 mg	**

**Daily Value not established

OTHER INGREDIENTS: Pea protein, vegetable magnesium stearate, and silicon dioxide, in a vegetable capsule composed of vegetable hypromellose and purified water.

Contains no: Gluten, soy, wheat, eggs, dairy, citrus, preservatives, artificial flavour or colour, or starch.

This product is non-GMO and vegan friendly.

Oocyte SAP contains 120 capsules per bottle.

DIRECTIONS FOR USE

Adult Women: Take 2 capsules twice daily with meals or as directed by your healthcare practitioner.

INDICATIONS

Oocyte SAP may help improve symptoms associated with PCOS and aid in the regularization of menstrual cycles in PCOS patients,* and can help:

- Promote oocyte health as well as improve ovulation and overall reproductive health.*
- Improve oocyte quality in patients with PCOS and infertility.*
- Promote mitochondrial function associated with oocyte quality.*
- Improve plasma lipid profile, improve insulin sensitivity and regulate glucose metabolism.*

CAUTIONS AND WARNINGS

Consult a healthcare practitioner prior to use if you are pregnant or breast-feeding; if you are taking blood pressure medication or blood thinners; if you have kidney stones; or if you have diabetes. For adult use only. Consult a healthcare practitioner prior to use to ensure the timely treatment of a serious cause of infertility.
Contraindication: Do not use this product if you are taking antibiotics or nitroglycerin.

PURITY, CLEANLINESS & STABILITY

All ingredients listed for each **Oocyte SAP** lot number have been tested by an ISO 17025 accredited third-party laboratory for identity, potency, and purity.

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

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FEMALE FERTILITY

Infertility is a medical concern worldwide, affecting 60–80 million couples (15% of couples of reproductive age). Female infertility is a contributing factor in about 50% of infertility cases, and is the focus of diagnosis in one-third of these cases.[1] A number of factors can contribute to female infertility, including obesity, psychological stress, environmental and occupational exposures, alcohol, and caffeine.[2] On a physiological level, abnormal levels of lipoproteins—such as an increase in low-density lipoprotein (LDL) cholesterol levels and a decrease in high-density lipoprotein (HDL) cholesterol levels—have been associated with reduced fecundability.[3] In addition to abnormal lipid profiles, an increase in oxidative stress is observed in patients suffering from PCOS, with higher levels of malondialdehyde (MDA) and superoxide dismutase (SOD).[4]

In more than 50% of infertile case diagnosis, ovulatory defects and unexplained causes are the most common etiologies.[5] Chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries are the main characteristics of PCOS, which is the most common endocrine disorder of reproductive-aged women.[6][7] PCOS has been linked to low-grade inflammation; disorders of glycolysis, pyruvate, and amino-acid metabolism; and abnormal lipid profile in follicular fluids.[8] Oocytes have the highest number of mitochondria and mitochondrial DNA copies of any cell.[9][10] Oocytes depend on energy produced by mitochondria via oxidative phosphorylation. Oocyte quality is largely determined by the status and function of mitochondria, and is crucial to the fertilization of the oocyte and development of the embryo. Specifically, low mitochondrial DNA negatively impacts oocyte quality in women suffering from ovarian insufficiency.[9][10] Continued embryogenesis and implantation is observed in embryos that develop from oocytes with higher ATP content.[11] Along with anovulation, PCOS is also characterized by ovulatory dysfunction, which correlates with an increased risk of endometrial hyperplasia and endometrial cancer.[7]

Treatments for ovulation, including administration of clomiphene citrate and induction of ovulation with gonadotropins, have their own disadvantages, such as high cost, need for constant monitoring, and further health complications.[12] There is hence a need for a more natural and effective therapeutic approach.

NUTRACEUTICALS IN THE MANAGEMENT OF FEMALE INFERTILITY

Coenzyme Q_{10} (CoQ_{10}) and PQ_{10}

Coenzyme Q_{10} is an antioxidant that scavenges free radicals, preventing oxidation of lipids and proteins in cells, and supporting cellular energy production.[13] Supplementation with CoQ_{10} in a rat animal model has been associated with preventing reduction of insulin receptor substrate-1 and p110-β, while inhibiting increase in IL-6.[14] In a randomized, double-blind, placebo-controlled trial of 40 women diagnosed with PCOS, administration of 100 mg/d of CoQ_{10} for 12 weeks improved gene expression related to insulin, lipid metabolism, and inflammation.[15] Similarly, other studies have corroborated the beneficial effects of CoQ_{10} on serum LDL cholesterol levels, glucose metabolism, and improvement in ovulation. Supplementation with 100 mg/d of CoQ_{10} in 30 women for 12 weeks resulted in a decrease in serum fasting glucose and improved insulin sensitivity, as well as altered total cholesterol and serum LDL cholesterol concentrations.[16] When 60 mg/d of CoQ_{10} was administered to 51 patients for 82 ovulation cycles, it was observed that CoQ_{10} worked synergistically with clomiphene citrate in improving ovulation and clinical pregnancy rates, as opposed to clomiphene citrate alone.[12]

The pea-emulsified CoQ_{10} form (PQ_{10}) is prepared by blending CoQ_{10} with an unique emulsifier—a specific pea protein. This protein is ideal for blending with CoQ_{10}, as it has both hydrophobic and hydrophilic components. The PQ_{10} form can help improve the absorption of CoQ_{10}.

Acetyl-L-Carnitine

Acetyl-L-carnitine is a known antioxidant, and has shown protective effects on growing embryos by scavenging free radicals.[17] Addition of acetyl-L-carnitine to embryo cultures challenged by oxidative stress triggers, such as hydrogen peroxide, has shown a reduction in DNA damage and an improvement in chromosomal structure and development of blastocysts.[18] Acetyl-L-carnitine is crucial for transporting long-chain fatty acids across the inner mitochondrial membrane for the process of β-oxidation. Acetyl-L-carnitine supplementation significantly reverses the age-associated decline of mitochondrial membrane potential, ameliorating oxidative mitochondrial decay and improving mitochondrial abnormalities.[19][20] Supplementation with acetyl-L-carnitine has also improved the cytoplasmic volume, and altered the lipid profile as well as the vesicle size of lamb oocytes.[21] A study observing serum total L-carnitine levels in 27 nonobese PCOS women found significantly low levels of L-carnitine and sex hormone–binding globulin (SHBG) in PCOS patients compared to healthy women, and low levels of L-carnitine were associated with hyperandrogenism and insulin resistance in PCOS patients.[22] In a randomized, controlled, double-blind clinical trial, 85 clomiphene-resistant PCOS patients who were administered 3 g of L-carnitine in addition to 250 mg clomiphene citrate daily showed improved ovulation, pregnancy rates, body mass index, and lipid profile compared to their counterparts who received only clomiphene citrate.[23]

N-Acetylcysteine

N-Acetylcysteine (NAC), naturally derived from L-cysteine, is known to improve insulin sensitivity and is a safe and effective treatment for PCOS. It acts by increasing secretion of insulin and improving insulin sensitivity.[24] NAC is a precursor to glutathione synthesis, which protects cells from oxidative damage and plays an important role in the development of embryos and cell proliferation.[25] A dose of 600 mg of NAC administered three times a day to 15 patients compared to metformin showed improvement in oocyte quality in a randomized, double-blinded, placebo-controlled trial carried over a period of six weeks.[26] Insulin sensitivity response was significantly improved in 31 lean and obese PCOS subjects administered with 1.8 g/d and 3 g/d of NAC over five or six weeks.[27]

R–alpha-Lipoic Acid

alpha-Lipoic acid has been linked with increased glucose uptake via increase in levels of adenosine monophosphate–activated protein kinase (AMPK), and has thus been used in therapeutic strategies for the management of endocrine disorders and diabetes. In a group of 32 PCOS obese patients administered 400 mg/d of *alpha*-lipoic acid for 12 weeks, an improvement in metabolic parameters such as body mass index and insulin sensitivity index was observed.[28] In another trial, use of *alpha*-lipoic acid in conjunction with *myo*-inositol in 36 obese PCOS patients improved metabolic parameters.[29] In addition, *alpha*-lipoic acid has shown a synergistic effect with *myo*-inositol in improvement of oocyte quality after three months of treatment.[29]

myo-Inositol

The benefits of *myo*-inositol in alleviating endocrine imbalances occurring in PCOS has been well-established.[30][31] Supplementation for 12 weeks with 2 g/d of *myo*-inositol in 50 overweight PCOS patients reduced hyperinsulinemia, improved insulin sensitivity, and restored balance in the levels of luteinizing hormone, prolactin, and testosterone.[30] An improvement in oocyte quality was observed in 175 IVF participants who were supplemented 4 g/d of *myo*-inositol from day 1 of their cycle to 14 days after embryo transfer. Pregnancy rates in groups supplemented with *myo*-inositol or *myo*-inositol plus melatonin were 36.7% and 41.4%, respectively, compared to the controls without *myo*-inositol, where the pregnancy rate was 31%.[31]

Mixed Tocopherols Concentrate

Vitamin E is a fat-soluble antioxidant that protects sensitive cell membranes by neutralizing free radicals.[32] Supplementation with vitamin E for women above 35 years of age has shown an improvement in the time to pregnancy for infertile couples over a range of doses, with an average of 37 mg/d from the time of conception up to live birth.[33] Vitamin E has also been associated with ovarian egg numbers and size, with the number and size of eggs increasing with higher antioxidant supplementation in animal models.[34]

Vitamin C

Vitamin C is a water-soluble antioxidant and a key cofactor in various biochemical processes necessary for the synthesis of biocomponents.[31] In a study looking at nutritional deficiencies of 54 women diagnosed with PCOS, over 70% of participants were found to have insufficient intake of vitamin C in their diets, among other vitamins.[35] Supplementation with 0.2 g vitamin C twice a day for three months, synergistically with other vitamins such as vitamin E, improved the symptoms of PCOS and aided in the regularization of menstrual cycles in PCOS patients.[36]

SYNERGISM FOR OPTIMAL EFFICACY

Evidence presented by systematic reviews suggests that supplementing a combination of key nutraceuticals such as acetyl-L-carnitine, *N*-acetylcysteine, vitamin C, vitamin E, CoQ_{10}, *myo*-inositol, and *alpha*-lipoic acid can effectively improve oocyte quality and embryo development, alleviate symptoms of PCOS, and maintain overall ovarian function.[16][25][29][34]

REFERENCES

1. American Pregnancy Association. *Female infertility.* · http://americanpregnancy.org/infertility/female-infertility/ · Updated 2017-05-16.
2. Sharma, R., et al. "Lifestyle factors and reproductive health: Taking control of your fertility." *Reproductive Biology and Endocrinology* Vol. 11 (2013): 66.
3. Pugh, S.J., et al. "Preconception maternal lipoprotein levels in relation to fecundability." *Human Reproduction* Vol. 32, No. 5 (2017): 1055–1063.
4. Kuscu, N.K., et al. "Oxidative stress but not endothelial function exists in non-obese, young group of patients with polycystic ovary syndrome." *Acta Obstetricia et Gynecologica Scandinavica* Vol. 88, No. 5 (2009): 612–617.
5. Talmor, A., et al. "Female obesity and infertility." *Best Practice & Research. Clinical Obstetrics & Gynaecology* Vol. 29, No. 4 (2015): 498–506.
6. Legro, R.S., et al. "Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome." *The Journal of Clinical Endocrinology and Metabolism* Vol. 100, No. 11 (2015): 4048–4058.
7. Goodman, N.F., et al. "American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome—Part 1." *Endocrine Practice* Vol. 21, No. 11 (2015): 1219–1300.
8. Zhang, Y., et al. "Follicular metabolic changes and effects on oocyte quality in polycystic ovary syndrome patients." *Oncotarget* Vol. 8, No. 46 (2017): 80472–80480.
9. Cummins, J.M., et al. "The role of mitochondria in the establishment of oocyte functional competence." *European Journal of Obstetrics, Gynecology, and Reproductive Biology* Vol. 115, Suppl. 1 (2004): S23–S29.
10. Mary-Panlioup, P., et al. "Low oocyte mitochondrial DNA content in ovarian insufficiency." *Human Reproduction* Vol. 20, No. 3 (2005): 593–597.
11. van Blerkom, J., et al. "ATP content of human oocytes and developmental potential and outcome after in-vitro fertilization and embryo transfer." *Human Reproduction* Vol. 10, No. 2 (1995): 415–424.
12. Refaeey, A., et al. "Combined coenzyme Q_{10} and clomiphene citrate for ovulation in clomiphene-citrate-resistant polycystic ovary syndrome." *Reproductive Biomedicine Online* Vol. 29, No. 1 (2014): 119–124.
13. Papucci, L., et al. "Coenzyme Q_{10} prevents apoptosis by inhibiting mitochondrial depolarization independently of its free radical scavenging property." *The Journal of Biological Chemistry* Vol. 278, No. 30 (2003): 28220–28280.
14. Tarry-Adkins JL., et al. "Coenzyme Q_{10} prevents insulin signaling dysregulation and inflammation prior to development of insulin resistance in male offspring of a rat model of poor maternal nutrition and accelerated postnatal growth." *Endocrinology* Vol. 156, No.10 (2015): 3528–3537.
15. Rahmani, E., et al. "The effect of coenzyme Q_{10} supplementation on gene expression related to insulin, lipid and inflammation in patients with polycystic ovary syndrome." *Gynecological Endocrinology* Vol. 34, No. 3 (2018): 217–222.
16. Samimi, M., et al. "The effects of coenzyme Q_{10} supplementation on glucose metabolism and lipid profiles in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial." *Clinical Endocrinology* Vol. 86, No. 4 (2017): 560–566.
17. Gulcin, I., et al. "Antioxidant and antiradical activities of L-carnitine." *Life Sciences* Vol. 78, No. 8 (2006): 803–811.
18. Abdelrazik, H., et al. "L-Carnitine decreases DNA damage and improves the in vitro blastocyte development rate in mouse embryos." *Fertility and Sterility* Vol. 91, No. 2 (2009): 589–596.
19. Ames, B.N., and J. Liu. "Delaying the mitochondrial decay of aging with acetylcarnitine." *Annals of the New York Academy of Sciences* Vol. 1033 (2004): 108–116.
20. Kathirvel, E., et al. "Acetyl-L-carnitine and lipoic acid improve mitochondrial abnormalities and serum levels of liver enzymes in a mouse model of nonalcoholic fatty liver disease." *Nutrition Research* Vol. 33, No. 11 (2013): 932–941.
21. Reader, K.L., et al. "Effects of acetyl-L-carnitine on lamb oocyte blastocyte rate, ultrastructure, and mitochondrial DNA copy number." *Theriogenology* Vol. 83, No. 9 (2015): 1484–1492.
22. Fenkci, S.M., et al. "Serum total L-carnitine levels in non-obese women with polycystic ovary syndrome." *Human Reproduction* Vol. 23, No. 7 (2008): 1602–1606.
23. Ismail, A.M., et al. "Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial." *European Journal of Obstetrics, Gynecology, and Reproductive Biology* Vol. 180 (2014): 148–152.
24. Ammon, H.P.T., et al. "Cysteine analogues potentiate glucose-induced insulin release in vitro." *Diabetes* Vol. 35, No. 12 (1986): 1390–1396.
25. Truong, T.T., et al. "Antioxidants improve mouse preimplantation embryo development and viability." *Human Reproduction* Vol. 31, No. 7 (2016): 1445–1454.
26. Cheraghi, E., et al. "*N*-Acetylcysteine compared to metformin, improves the expression profile of growth differentiation factor-9 and receptor tyrosine kinase c-kit in the oocytes of patients with polycystic ovarian syndrome." *International Journal of Fertility & Sterility* Vol. 11, No. 4 (2018): 270–278.
27. Fulghesu, A.M., et al. "*N*-Acetyl-cyteine treatment improves insulin sensitivity in women with polycystic ovary syndrome." *Fertility & Sterility* Vol. 77, No. 6 (2002): 1128–1135.
28. Genazzani, A.D., et al. "Modulatory effects of *alpha*-lipoic acid (ALA) administration on insulin sensitivity in obese PCOS patients." *Journal of Endocrinological Investigation* (2017). doi: 10.1007/s40618-017-0782-z [Epub ahead of print].
29. Ragp, R., et al. "Effect of *myo*-inositol and *alpha*-lipoic acid on oocyte quality in polycystic ovary syndrome non-obese women undergoing in vitro fertilization: A pilot study." *Journal of Biological Regulators and Homeostatic Agents* Vol. 29, No. 4 (2015): 913–923.
30. Artini, P.G., et al. "Endocrine and clinical effects of *myo*-inositol administration in polycystic ovary syndrome." *Gynecological Endocrinology* Vol. 29, No. 4 (2013): 375–379.
31. Pacchiarotti, A., et al. "Effect of *myo*-inositol and melatonin versus *myo*-inositol, in a randomized controlled trial, for improving in vitro fertilization of patients with polycystic ovarian syndrome." *Gynecological Endocrinology* Vol. 32, No. 1 (2016): 69–73.
32. Ahmadi, S., et al. "Antioxidant supplements and semen parameters: An evidence based review." *International Journal of Reproductive Biomedicine* Vol. 14, No. 12 (2016): 729–736.
33. Ruder, E.H., et al. "Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility." *Fertility and Sterility* Vol. 101, No. 3 (2014): 759–766.
34. Barim-Oz, Ö., et al. "The influence of dietary antioxidant on ovarian eggs and levels of vitamin E, C, A, astaxanthin, β-carotene and oxidative stress in tissues of *Astacus leptodactylus* (Eschscholtz) during reproduction." *Cellular and Molecular Biology* Vol. 62, No. 14 (2016): 1–10.
35. Szczuko, M., et al. "Quantitative assessment of nutrition in patients with polycystic ovary syndrome (PCOS)." *Roczniki Państwowego Zakładu Higieny* Vol. 67, No. 4 (2016): 419–426.
36. Zhang, D., et al. "The effects of oxidative stress to PCOS." *Sichuan Da Xue Xue Bao. Yi Xue Ban* Vol. 39, No. 3 (2008): 421–423.

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