The Best-in-Class Nutritional Pre-Conception Supplement For Healthy Sperm

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Abstract

We present the "birth certificate" of a new class of nutritional supplements led by AlphaSperm. This doctor-formulated, antioxidant, mineral (coenzyme), amino acid, micronutrient and herbal supplement is specifically developed to create healthier sperm and thereby improve men's fertility potential and the likelihood of healthy babies.

INTRODUCTION

The relationship between overall health and male fertility.

It has become clear over the last several decades that good overall health is important for optimal male fertility. It is also now recognized that reproductive health is a "biomarker" of overall health. Overall health is governed by lifestyle and diet choices, along with environmental and genetic influences. Lifestyle choices such as the use of marijuana, alcohol and tobacco have been shown to impair both overall health and male reproductive health. Likewise, diet choices that lead to obesity, dyslipidemia and cardiovascular disease based on poor nutritional balance also negatively affect male fertility potential.

The relationship between nutrition and male fertility.

Reactive oxygen species (ROS, oxidants) are the body's molecular messengers that play important roles in normal cell function, cell-to-cell signaling, and in detoxification processes. When release of ROS exceeds the antioxidant capacity, termed oxidative stress, this leads to cellular dysfunction and cell death. Oxidative stress is a causative factor for many health disorders and conditions including cancers, heart disease (Debois et al, 2020) and autoimmunity. It is also estimated that 40% of male infertility is due to imbalances in oxidative health. Diet and nutritional choices are a key component to maintaining oxidative balance for both general and reproductive health. The best diets for maintaining oxidative balance and promoting good cardiovascular and general health are the "heritage" diets that include Mediterranean and Paleo depending on whether you seek to go back 33 generations or 333 generations of human existence. They are both rich in fruits, vegetables, nuts, leafy greens and minimize carbohydrates from bread, rice and pasta. Although the benefits of antioxidant-rich diets to optimize health have been demonstrated, conclusive scientific evidence that either of these diets are superior in optimizing male fertility potential has yet to be delineated.

Current evidence supporting male preconception supplement use.

The lack of adequate antioxidants found in the typical Western diet is well known. And although an "ideal" antioxidant diet is known for overall health and longevity, whether that same diet also optimizes male fertility potential is currently an assumption, albeit a very reasonable one. What has been debated recently is whether antioxidant nutritional supplements can improve male fertility. One highly relevant issue concerning the studies addressing this are the outcomes that are evaluated. Indeed, studies that examine the effect of antioxidants on semen parameters (i.e. the semen analysis) span the entire spectrum from no benefit to benefit (ESHRE, 2018; Majzoub and Agarwal 2018). The most consistently demonstrated benefit is that of increasing sperm motility. However meta-analyses that have examined the effects of male antioxidants on actual fertility (i.e. pregnancy) have consistently concluded that there is benefit to male antioxidant supplementation (Table 1).

Table 1. Published Cochrane Meta-Analytical Reviews of Male Antioxidants and Pregnancy Outcomes

Published Reference	Studies & Couples / men	Pregnancy Rate (CI)	Miscarriage Rate (CI)
Cochane, 2011	34 studies 2876 couples	**OR 4.18** (CI, 2.6-6.6)	**OR 4.85** (CI, 1.9-12.4)
Cochane, 2014	48 studies 4179 couples	**OR 3.43** (CI, 1.9-6.1)	**OR 4.21** (CI, 2.0-8.5)
Cochane, 2019	61 studies 6164 couples	**OR 2.97** (CI, 1.9-4.63)	**OR 1.79** (CI, 1.2-6.7)
Cochane, 2022	90 studies 10,103 men	**OR 1.89** (CI, 1.45-2.47) **Live Birth**	**OR 1.46** (CI 0.75-2.83)

A reasonable conclusion from the evidence surrounding these two distinctly different outcomes is that antioxidants improve human fertility through mechanisms or pathways that may not be obviously ascertained from the semen analysis. Two such recently described mechanisms include sperm DNA fragmentation and sperm epigenetics (Sakkas and Alvarez, 2010; Aston et al, 2015; Denham et al 2015; Donkin and Barres, 2018) which are both known to impair sperm function in the absence of an effect on the routine semen analysis. In other words, in the future we will need to take a "deeper dive" with sperm when assessing the effects of nutritional supplements on male fertility potential.

THE DESIGN OF A MALE PRECONCEPTION SUPPLEMENT

Given the underlying poor antioxidant quality of the Western diet, along with conflicting evidence of effects of antioxidants on semen parameters, but positive evidence that antioxidant supplements improve pregnancy rates, the idea of a male pre-conception ("pre-prenatal") nutritional supplement is certainly valid and merits pursuit. In fact, considering only improvements in conception and miscarriage rates, the benefits of a well-designed male pre-conception supplement could match or even exceed the value of the decades-old national recommendation for women to take prenatal supplements that include folic acid to prevent fetal neural tube defects (https://www.cdc.gov/preconception/planning.html).

The intentional design of AlphaSperm as a male preconception supplement.

Based on these principles, AlphaSperm was developed as the birth certificate product representing a new concept in nutritional supplements: A male preconception formula to create "healthy" sperm. And from what we currently understand, healthy sperm is not always measured by the routine semen analysis, but by enhancing sperm fertility potential through other critical pathways such as sperm DNA fragmentation and epigenetic enhancement. The question asked and answered by its inventors, similar to the creation of essential foods for astronauts in space, is how do we distill the essentials of a balanced diet into a nutritional supplement to promote optimal male fertility? We believe that AlphaSperm has bottled the essential dietary ingredients for male reproductive health.

AlphaSperm composition is based on the following 6 nutritional principles:

- To supply substances that are essential for health but unable to be made by the body.
- To dispense nutritional ingredients that support sperm health and that may be readily available in a balanced diet but are deficient in a unbalanced or typical diet.
- To provide a broad and comprehensive range of antioxidants to combat the known effects of oxidative stress on sperm and fertility.
- To supply balanced dosages of micronutrients and minerals that avoids the detrimental effects of their associated excesses (i.e. megadosing) or deficiencies.
- To include ingredients with the strongest medical evidence (ideally randomized, controlled clinical trials) of having an effect on sperm or male fertility.
- To combine herbal and other traditional remedies that have known macro-level, adaptogenic effects of reducing stress and promoting overall and sexual well-being.

Arguments for naturally-sourced nutritional supplements.

AlphaSperm has intentionally focused on the use of naturally-sourced ingredients in its novel supplement design. Naturally sourced supplements often contain wider nutrient complexity, which can lead to better absorption and bioavailability. Natural supplements typically come from whole foods, and thereby are less likely to contain artificial additives, synthetic chemicals, fillers, or excessive amounts of isolated nutrients that might be associated with health risks. This reduces the risk of overdosing or imbalance of specific nutrients. Importantly, it has been demonstrated that for many vitamins including vitamins A, E, and K, and the phenolic antioxidants, body absorption or uptake is superior with natural versus synthetic formulations (Burton et al, 1998. Damiani et al, 2009). In fact, most studies that compare natural versus synthetic nutritional supplements reveal that synthetics may at times equal, but typically never exceed, the absorption rates of natural supplements. Whole-food supplements also often offer a broader spectrum of nutrients compared to synthetic counterparts. Finally, there are proponents who argue that consuming nutrients in natural forms could have long-term health and well-being benefits beyond meeting basic nutritional needs.

Arguments for naturally-sourced fillers or excipients.

AlphaSperm has intentionally focused on the use of naturally-sourced excipients in its novel supplement design. Excipients or fillers are substances added to supplements and medications to help with manufacturing, stability, appearance, and palatability of the product. They can be of natural or synthetic origin. Commonly, inorganic chemicals such as magnesium stearate are used as synthetic fillers in supplements. The advantages of naturally source excipients include the fact that they are perceived as safer by consumers since they come from natural sources and are more likely to have a history of safe use (i.e. Kosher products). Natural excipients can be more compatible with various vitamins and minerals, potentially leading to better stability, fewer interactions, less toxicity, and more controlled release. Natural excipients often contain compounds that synergize with vitamins, potentially enhancing accessibility, absorption and effectiveness and transformation of the active ingredient. This has been shown to be the case for vitamins A, C, D, E, and K and coenzyme Q10 (CoQ-10) (Lopez-Lluch et al, 2019). In fact, there is entire new discipline of nutrition research that focuses on the development of “food matrices” to optimize nutritional value of supplements (McClements et al, 2015).

AlphaSperm vitamin content

Considered the major "antioxidant group," **vitamins A, C and E** are found in 10-fold higher doses in semen than blood. They are work horses in controlling what's called "oxidative stress" in sperm. Sperm are very small, very high-energy cells that move rapidly, which is very unique in the body. Due to their compact design, the sperm engines (mitochondria) are located right next to the delicate DNA payload. The free radicals that are generated from the energy of sperm movement are sources of "oxidative stress" and can easily damage the DNA payload, and result in infertility. Antioxidants vitamins A, C and E are great at absorbing the radical oxygen species and free radicals that are generated in sperm.

There are eight described **B vitamins** and all eight are found in AlphaSperm. All B vitamins are water-soluble and, as the body does not store them, they all need to be replaced daily. They are not made by the body and need to be sourced through food. B vitamins are found in animal proteins, dairy products, leafy green vegetables, nuts, eggs and beans. Their functions generally involve metabolism and energy production **(B1 or thiamin; B2 or riboflavin; B7 or biotin)** serving as cofactors for nerve and brain health **(B5 or pantothenic acid; B6)**, and are intricately involved in RNA, DNA and red blood cell synthesis **(B3 or niacin; B9 or folic acid; B12)**. Regarding sperm health, most B vitamins serve as excellent antioxidants but other specific roles include: Co-enzyme A production by B5 which is necessary for sperm metabolism; hormonal regulation of sperm production and sperm motility support (B6); support of sperm count and production (B6); regulation of sperm maturation and proper DNA synthesis and repair in sperm (B9; B12); B vitamin deficiencies are associated with known disease states (Beriberi, anemia, Pellagra, neuropathy, Brittle hair syndrome) and any B vitamin deficiency can negatively affect mitochondrial metabolism of amino acids, glucose, and fatty acids.

Importantly, **vitamin B9 or folate** is water soluble and only available from our diet. In addition, the active form of folate used by the body is methyltetrahydrofolate (MTHF), which is the reduced form of folate. Unfortunately, about 40% of humans worldwide are unable to reduce folate to MTHF efficiently and are therefore at risk of folate deficiency and adverse health outcomes. For this reason, AlphaSperm provides vitamin B9 in its fully reduced and readily absorbed form (5-MTHF). **Choline** is an essential micronutrient similar to the B vitamins that provides methyl groups needed for many metabolic pathways but most importantly those involved in cell membrane formation. As spermatogenesis is one of the most rapidly dividing tissues in the body, producing 1000 sperm per heartbeat, choline is essential for healthy sperm production and is found in AlphaSperm.

ALPHASPERM NUTRITIONAL COMPOSITION

Similar to a timeless musical score, the composition of a nutritional supplement is of fundamental importance to its impact. Based on our knowledge of the biology of sperm production, AlphaSperm is composed of 4 types of compounds: vitamins, minerals and micronutrients, amino acids and herbal supplements.

Vitamin D is needed to build and maintain healthy bones by allowing the body to absorb calcium. Rickets is a disease of bone that stems from vitamin D deficiency. As calcium is important for other body functions, normal vitamin D levels also support immune health, muscle function and brain activity. Several studies have now shown a relationship between vitamin D levels and sperm counts, motility and DNA fragmentation, suggesting its importance for sperm production and quality (Blomberg et al, 2011; Güngör et al, 2022). Vitamin K is critical for making proteins involved with normal blood clotting, wound healing and bone growth. Vitamin K is also present throughout the testes, and in animal studies vitamin K deficiency impairs sperm production which lowers sperm counts and increases the proportion of sperm with abnormal morphology (Sanyaolu et al, 2019).

AlphaSperm mineral and micronutrient content

Selenium is a mineral critical for the development of sperm motility and is a major determinant of normal sperm shape or morphology. It is also a nonenzymatic antioxidant. Dr Turek published the only randomized, controlled trial in humans that examined the effect of high and low selenium levels on sperm motility (Hawkes et al, 2001). The incorporation of selenium in Alpha Sperm is based on this research. **Iodine** is an essential mineral for normal thyroid function. Normal thyroid function is also important for normal male fertility. A recent large association study has determined that both low and high levels of iodine correlated with lower sperm counts among infertile men (Wang et al, 2021). **Zinc** is essential in spermatogenesis as it is a cofactor for DNA transcription and steroid receptors. Although a randomized clinical trial involving zinc failed to show that its supplementation increased live birth rates (Schisterman et al, 2019), zinc's high concentration in semen (30 times higher than in blood) suggests its importance to male fertility may likely be through its antioxidant and antibacterial functions. **Magnesium** is an essential mineral cofactor that is involved in more than 300 of the body's enzyme systems ranging from protein synthesis to energy production. In sperm, one of the few motile cells in the body, available energy is essential and the formation of the critical energy molecule ATP is a magnesium intensive process (Morisawa et al, 1982). In animals, magnesium deficiency dramatically reduces sperm production and motility. **Copper** is an essential trace mineral that also helps to make energy as well as connective tissue and blood vessels. In its free, unbound form, copper is toxic to sperm (copper IUDs) but when bound as a coenzyme it is critical for DNA mitosis and meiosis during spermatogenesis. **Manganese** is another essential trace mineral that is found mostly in bones, liver, kidneys, and pancreas. It helps the body form connective tissue, blood clotting factors, and is important for the sex hormones that drive sperm production. **Chromium (III; picolinate)** is yet another trace essential mineral that enhances the action of the hormone insulin and is involved in the absorption of carbohydrate, proteins, and fats. Although Chromium VI is a reproductive toxin found in industrial waste, chromium III in AlphaSperm is considered an essential mineral and plays a role in sperm DNA synthesis and acts as an antioxidant. **Molybdenum** is another essential mineral found in AlphaSperm that is an important cofactor in 4 important enzyme systems in the body that break

down waste products and old DNA within cells. In animal models, molybdenum affects sperm quality through its modulation of oxidative stress (Zhai et al, 2013).

Coenzyme Q10 (CoQ10; ubiquinone) is a powerful, lipid-based, micronutrient antioxidant found in almost every cell in the body. Its main role involves neutralizing free radicals that can damage cell membranes and DNA. Its role in supporting male fertility is now clear as CoQ10 supplementation improves the antioxidant capacity of semen which protects sperm DNA from oxidative damage and subsequent DNA fragmentation. A recent large systemic review concluded that it has beneficial effects on seminal quality, and especially sperm motility, as well as sperm DNA chromatin integrity (Salvio et al, 2021). **Resveratrol** is a plant-base, polyphenol, micronutrient derived from grape and berry skin that has well-established antioxidant properties. It is believed that polyphenols in red wine might have health benefits and these compounds have been implicated to explain why the French have low rates of cardiovascular disease despite high cholesterol and saturated fat diets, otherwise known as the "French Paradox" (Ferrieres, 2004). In sperm, resveratrol supplementation has been shown to have positive effects on mitochondrial function and membrane function and a prospective study of repeated measures design among men with idiopathic male infertility demonstrated significant increases in both sperm counts and motility after resveratrol supplementation for 6 months (Illiano et al, 2020). **Lycopene** is a tomato plant-derived, carotenoid, macronutrient that is one of the most powerful known antioxidants and has been extensively studied in cancers and heart disease. Recently, a randomized, double blind, placebo-controlled trial conducted on (n=44) infertile men with low sperm counts demonstrated a significant increase in ejaculate volume, sperm concentration, total sperm counts and motility in the lycopene group compared to controls (Nouri et al, 2019).

One of the newest and best studied micronutrients is **Alpha-lipoic acid (ALA)**. As an important mitochondrial coenzyme and key component of the Kreb cycle and ATP synthesis, ALA is a strong antioxidant that has been shown to improve oxidative stress both in vitro and in vivo. A recent randomized, triple-blind, placebo-controlled clinical trial revealed that sperm concentrations, total sperm counts, sperm motility and semen total antioxidant capacity were significantly higher in ALA subjects than in controls (Haghighian et al, 2019). Inositol is a cyclical, carbohydrate macronutrient that plays an important role in hormone production and intracellular signaling throughout the body, but especially in the brain. Notably, its concentration is significantly higher in the testis seminiferous tubules than in the blood and is thought be involved in the regulation of sperm motility, capacitation and acrosome reaction. In vitro studies that expose sperm to inositol shows that it improves sperm motility, likely through beneficial effects on mitochondrial function (Ghasemi et al, 2019). A recent double-blind, placebo-controlled study of men with idiopathic infertility showed that inositol significantly increased sperm concentration, total sperm count, progressive motility and the number of acrosome-reacted sperm compared to placebo. In addition, beneficial effects on reproductive hormones

were compared to placebo. In addition, beneficial effects on reproductive hormones were also noted (Calogero et al, 2015).

AlphaSperm amino acid content

L-Arginine is an essential amino acid that is important for nitric oxide synthesis in sperm and plays an important role in sperm metabolism, maturation and sperm DNA-packaging quality. It also contributes to the antioxidant activity in semen. **Acetyl-L-Carnitine** is a naturally occurring, water-soluble amino acid derived antioxidant that is highly concentrated in sperm and in the epididymis. It is involved with sperm metabolism as a source of bioenergetic "fuel' for sperm motility, especially after sperm leave the testicle and enter the epididymis for further maturation. Among infertile men with varicocele or documented genital tract inflammation, a randomized controlled trial of acetyl-L-carnitine led to significant improvements in sperm motility (Lenzi et al, 2004). **L-Cysteine** is a semiessential amino acid that is both a powerful antioxidant and is also converted to the major antioxidant glutathione. **L-Glutathione** is a complex amino acid and likely the most powerful and famous of all antioxidants in the body, earning Frederick Hopkins a Nobel Prize in 1929 for its chemical elucidation. In most cells, it protects the plasma membrane from lipid peroxidation, scavenges superoxide and prevents oxygen formation. In sperm, a glutathione deficiency leads to increased lipid peroxidation and instability of the sperm's mid piece resulting in defective motility (Ursini et al, 1999).

L-cysteine is considered a conditionally essential amino acid and antioxidant which is derived from methionine and serves as a building block to the master antioxidant L-glutathione. **L-Methionine** is another (essential) amino acid antioxidant that helps to detoxify harmful substances in the body, including heavy metals. It is also a source of donor methyl groups critical to proper epigenetic programming of sperm DNA (Townsend et al, 2023).

AlphaSperm herbal content

Ashwagandha has been used for thousands of years in Ayurvedic medicine. It is well-known for its rejuvenating and adaptogenic properties (adaptogens are substances that increase the body's ability to cope with both physical and mental stresses). Observational studies suggest that ashwagandha in men leads to increases in testosterone levels, improved sperm quality, and higher antioxidant levels (Mahdi et al, 2011). In a study of overweight men aged 40-70, testosterone levels increased after taking an ashwagandha for 8 weeks (LoPresti et al, 2019). The mechanism is thought to be that its apoptogenic properties reduce stress, and thereby lowering cortisol, a classic testosterone "stealing" hormone. **Maca root (L. meyenii)** is an Andean plant in the mustard family, it was first isolated and cultivated in Peru over 2000 years ago. Maca root has been ascribed many medicinal properties, including improving sexual desire and erectile function in men. We have included this herbal supplement in AlphaSperm to support the sexual health of men trying to conceive. **Astralagus Root Extract (Milk Vetch)** is

a bean-derived flavenoid that has been shown to promote immunity, act as an antiinflammatory and oxidative quencher and promote cell proliferation. It has also been demonstrated to dramatically improve human sperm motility in vitro. Derived mainly from tomatoes, and essential for photosynthesis in many plants, **lycopene** is an extremely powerful oxidant-quencher that is found in high concentrations in the testicle and in the semen. Lower lycopene levels in semen have been shown to correlate with male infertility.

CONCLUSION

There is no question that 40 years after the introduction of female prenatal supplements, significant scientific and clinical evidence now supports the concept of male pre-conception supplements to promote fertility and healthy offspring. AlphaSperm is the comprehensive birth-certificate formula for this new class of nutritional supplements and its composition is based on the best understood theory and clinical science known today.

† 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.

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