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Nutrition And Reproduction: Is There Evidence To Support A “Fertility Diet” To Improve Mitochondrial Function?

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Abstract

Normal function of mitochondria plays an essential role in enabling reproductive capacity. To date, few studies have investigated the role of promoting mitochondrial health in relation to fertility in humans. Selected nutritional interventions have demonstrated a potential to enhance mitochondrial function, suggesting a promise for future research for fertility treatment. This review summarizes the extant literature and highlights a putative role of particular nutrients in promotion of mitochondrial function, including in vitro, animal and human studies. Strong basis exists to advocate for further investigation of nutritional treatments for infertility patients.

Keywords

nutrition; fertility; mitochondria; obesity; supplement

Female obesity is associated with significant alterations in reproductive health and fertility. Not only does obesity decrease the likelihood of ovulation, it also significantly reduces the chance for pregnancy in women who ovulate regularly [1]. These data are of particular concern given the ongoing obesity epidemic and its effects on reproductive-age women [2]. Furthermore, women on the extremes of body mass spectrum suffer from subfertility, implicating nutrition in cases of both underweight and overweight women [3]. Modifications

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Contributors and their role

Katherine Shaum is the first author. She and the senior author made an outline for the manuscript together. Ms. Shaum did most of the literature search and wrote the first draft of the paper and completed submission of the paper.

Alex Polotsky is the senior author. He and the first author did the outline for the paper together. He assisted with the literature search and edited drafts of the manuscript. He also approved the final draft of the paper.

Competing Interest

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of dietary risk factors for ovulatory dysfunction have been advocated as the first line intervention for patients seeking treatment of infertility [4]. Consequently, nutrition is a key area of interest and potential non-pharmacological intervention for infertility patients. This review will examine the current literature pertaining to nutrients that have been linked with mitochondrial function and have a potential to impact fertility.

Nutrition And Reproduction: Data Indicate That No One Diet Can Be Billed As A One-For-All “Fertility” Pill

Infertility caused by specific dietary deficiencies may benefit from straightforward addition of missing components to the diet. However, in most cases dietary supplementation with the aim of boosting fertility has failed to produce definitive results. US Nurses' Health Study has shown increased risk of ovulatory dysfunction associated with many dietary factors, including protein intake, dietary fats, carbohydrates, alcohol, caffeine, and dairy [4]. The type of dietary protein may affect the risk of ovulatory infertility, as women who consume more vegetable vis-a-vis animal sources of protein demonstrated lower rate of infertility (relative risk 1.39 with high animal protein intake vs. 0.78 for those who consume more vegetable protein) [5]. Further, dietary glycemic index has been positively correlated with ovulatory infertility (risk ratio 1.92 for those with high glycemic load diet); whereas intake of vitamins has been inversely correlated with ovulatory infertility (relative risk 0.59 for women consuming 6 or more tablets per week) [5, 6]. The wide array of dietary influences on ovulatory dysfunction suggests a complex balance of nutrition for optimal fertility and confirms the dictum that there is no “one size fits all” dietary intervention to boost fertility.

Obesity And Impaired Mitochondrial Function Of The Oocyte

Animal models of obesity and diabetes have highlighted oocyte dysfunction in these diseases. Murine models of diabetes have demonstrated an increase in granulosa cell apoptosis and impaired oocyte maturation [7]. In this setting, apoptosis directly involves mitochondria, thus implying that the organelle that is nicknamed “the energy center of the cell” is intimately involved in oocyte maturation and follicular function. Obesity has been shown to be associated with decrease in oocyte quality [2]. Recent data suggests that in obesity and some associated conditions (such as polycystic ovary syndrome), a significant number of morphologically normal oocytes may be altered at the molecular level [2]. It may be particularly relevant that genes coding for oocyte factors responsible for chromosome alignment and segregation during meiosis are differentially expressed in women with PCOS [2]. Similarly, a mouse model of maternal obesity also demonstrated high incidence of spindle abnormalities as well as increased reactive oxygen species (ROS) generation in oocyte mitochondria [8].

Human studies confirm some of the information gathered from animal models of disease that implicate altered mitochondrial function in infertility. Studies of oocytes from obese women undergoing in vitro fertilization indicate that abnormal lipid accumulation and oxidative stress are associated with impaired oocyte development [9, 10]. Thus, there is a strong biological plausibility for seeking to improve mitochondrial function for fertility enhancement.

Is There Data To Support Dietary Interventions To Improve Mitochondrial Function?

Mitochondrial dysfunction has been implicated in many disease states including obesity and cardiovascular disease [11, 12]. Aging in particular has considerable mitochondrial implications, as it is associated with diminished function of key mitochondrial enzymes [13]. Aberrant mitochondrial function, such as decreased membrane oxidation and electron transport chain dysfunction have been demonstrated in diabetes and metabolic syndrome [12, 14, 15]. Mouse models of Alzheimer's disease show damage in mitochondria of vascular endothelial cells, a likely source of reactive oxygen species and oxidative damage to neurons [16]. Furthermore, myocardium is particularly sensitive to reactive oxygen species, implicating a role for mitochondrial function in various cardiomyopathies [14]. Thus, the role of mitochondria in multiple disease states warrants investigation into the role of dietary interventions to improve mitochondrial function.

Ability Of Dietary Interventions To Improve Mitochondrial Function

Previous studies in the area of mitochondrial nutrients have defined mitochondrial nutrients as “those which protect the mitochondria from oxidative damage and improve mitochondrial function”[15]. This definition can be further broken down into subcategories of antioxidants, cofactors and energy enhancers. Antioxidants are substances that scavenge free radicals to reduce the detrimental effects of reactive oxygen species on cell components. Cofactors enhance and enable proper mitochondrial metabolism by supplying a necessary component to metabolic pathways. Energy enhancers augment metabolism by repairing mitochondria and increasing mitochondrial biogenesis. Many nutrients fall into multiple categories [15].

The idea of a “mitochondrial diet” suggests that by supplementing necessary cofactors, energy enhancers and antioxidants into a diet, one might be able to boost mitochondrial function in various tissues to ultimately impact the entire organism. Many cofactors and coenzymes that are necessary for the chemical reactions that occur in the mitochondria are found in diet. Antioxidants, while not directly necessary for chemical reactions, might be beneficial as they function to reduce accumulation of reactive oxygen species, harmful byproducts of oxygen metabolism that have the potential to damage intracellular proteins and mitochondrial membranes [17, 18]. Cofactors, energy enhancers and antioxidants important in nutrition today include CoenzymeQ10 (also known as ubiquinol), Vitamin C, Vitamin E, Vitamin B6, Selenium, Catechins, Carnitine, Proanthocyanidins, Alpha-lipoic acid, and others [17]. Table 1 summarizes the current state of knowledge on the nutrients that have been investigated the most.

Where Do We Go From Here?

Studies investigating the role of cofactors such as carnitine and CoQ10 demonstrated benefit in many organ systems of animals receiving supplementation. Both of these supplements also showed some promise when studied in humans, each demonstrating the ability to improve mitochondrial function and decrease oxidative damage. Of particular interest, these supplements have potential beneficial effects on reproductive cells, including sperm and

oocytes. Studies of antioxidants, such as catechins, N-acetylcysteine, proanthocyanidins, and vitamin E have also demonstrated benefit to mitochondrial function in several organ systems. While numerous in vitro and animal studies have shown significant benefit to mitochondrial parameters with each of these antioxidants, the data available on humans is scarce, making it difficult to determine efficacy and safety. However, those studies that have been performed in humans show an overall trend of improved mitochondrial function and benefit to patients with antioxidant supplementation. N-acetylcysteine and Omega-3 fatty Acids have shown some promise for reproductive tissues, increasing the potential relevance in the treatment of subfertility.

At this time, the preponderance of available evidence is pre-clinical. While the impact on many nutrients of mitochondrial structure and function is seen in rodents, this may or may not be directly transferable to mammals with menstrual cycles. Endocrine control of menstrual and estrous cycles differs in some key regulatory aspects between the animal models used for most studies and human physiology. Use of non-human primates would provide more insight on the potential of specific nutrients to enhance fertility in menstrual mammals via improvements in mitochondrial functioning. Overall, the benefits shown in supplementation of mitochondrial nutrients in animal and in vitro studies seem sufficient to encourage further studies. While more research is needed to investigate the safety and efficacy of mitochondrial nutrients in fertility, this represents a promising area of interests for patients seeking help with conception.

REFERENCES

1. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. *Hum Reprod.* 2007; 22(2):414–420. [PubMed: 17095518]
2. Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. *Am J Obstet Gynecol.* 2010; 203(6):525–530. [PubMed: 20739012]
3. Rich-Edwards JW, et al. Physical activity, body mass index, and ovulatory disorder infertility. *Epidemiology.* 2002; 13(2):184–190. [PubMed: 11880759]
4. Chavarro JE, et al. Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstet Gynecol.* 2007; 110(5):1050–1058. [PubMed: 17978119]
5. Chavarro JE, et al. Protein intake and ovulatory infertility. *Am J Obstet Gynecol.* 2008; 198(2): 210.e1–217.e1. [PubMed: 18226626]
6. Chavarro JE, et al. A prospective study of dietary carbohydrate quantity and quality in relation to risk of ovulatory infertility. *Eur J Clin Nutr.* 2009; 63(1):78–86. [PubMed: 17882137]
7. Chang AS, Dale AN, Moley KH. Maternal diabetes adversely affects preovulatory oocyte maturation, development, and granulosa cell apoptosis. *Endocrinology.* 2005; 146(5):2445–2453. [PubMed: 15718275]
8. Sarfati J, Young J, Christin-Maitre S. [Obesity and female reproduction]. *Ann Endocrinol (Paris).* 2010; 71(Suppl 1):S49–S53. [PubMed: 21237331]
9. Robker RL, Wu LL, Yang X. Inflammatory pathways linking obesity and ovarian dysfunction. *J Reprod Immunol.* 2011; 88(2):142–148. [PubMed: 21333359]
10. Wittemer C, et al. Does body mass index of infertile women have an impact on IVF procedure and outcome? *J Assist Reprod Genet.* 2000; 17(10):547–552. [PubMed: 11209534]
11. Pajuelo D, et al. Improvement of Mitochondrial Function in Muscle of Genetically Obese Rats after Chronic Supplementation with Proanthocyanidins. *Journal of Agricultural and Food Chemistry.* 2011; 59:8491–8498. [PubMed: 21726097]

12. Nicolson GL. Metabolic syndrome and mitochondrial function: molecular replacement and antioxidant supplements to prevent membrane peroxidation and restore mitochondrial function. *J Cell Biochem.* 2007; 100(6):1352–1369. [PubMed: 17243117]
13. Karlic H, et al. Dietary l-carnitine stimulates carnitine acyltransferases in the liver of aged rats. *J Histochem Cytochem.* 2002; 50(2):205–212. [PubMed: 11799139]
14. Pung YF, et al. Resolution of Mitochondrial Oxidative Stress Rescues Coronary Collateral Growth in Zucker Obese Fatty Rats. *Atherosclerosis, Thrombosis, and Vascular Biology.* 2012; 32:325–334.
15. Liu J, et al. Targeting mitochondrial biogenesis for preventing and treating insulin resistance in diabetes and obesity: Hope from natural mitochondrial nutrients. *Adv Drug Deliv Rev.* 2009; 61(14):1343–1352. [PubMed: 19716392]
16. Shenk JC, et al. The effect of acetyl-L-carnitine and R-alpha-lipoic acid treatment in ApoE4 mouse as a model of human Alzheimer's disease. *J Neurol Sci.* 2009; 283(1–2):199–206. [PubMed: 19342064]
17. Miquel J, et al. Menopause: a review on the role of oxygen stress and favorable effects of dietary antioxidants. *Arch Gerontol Geriatr.* 2006; 42(3):289–306. [PubMed: 16442644]
18. Yang Z, et al. Reactive oxygen species-mitochondria pathway involved in FV-429-induced apoptosis in human hepatocellular carcinoma HepG2 cells. *Anticancer Drugs.* 2011; 22(9):886–895. [PubMed: 21730822]
19. Yeste M, et al. A diet supplemented with L-carnitine improves the sperm quality of Piétrain but not of Duroc and Large White boars when photoperiod and temperature increase. *Theriogenology.* 2010; 73(5):577–586. [PubMed: 20022096]
20. Lenzi A, et al. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril.* 2004; 81(6):1578–1584. [PubMed: 15193480]
21. Sachan DS, Hongu N, Johnsen M. Decreasing oxidative stress with choline and carnitine in women. *J Am Coll Nutr.* 2005; 24(3):172–176. [PubMed: 15930482]
22. Vicari E, La Vignera S, Calogero AE. Antioxidant treatment with carnitines is effective in infertile patients with prostatovesiculopididymitis and elevated seminal leukocyte concentrations after treatment with nonsteroidal anti-inflammatory compounds. *Fertil Steril.* 2002; 78(6):1203–1208. [PubMed: 12477513]
23. Bentov Y, et al. The use of mitochondrial nutrients to improve the outcome of infertility treatment in older patients. *Fertil Steril.* 2010; 93(1):272–275. [PubMed: 19732879]
24. Löhre B, et al. N-acetylcysteine impairs survival of luteal cells through mitochondrial dysfunction. *Cytometry A.* 2010; 77(4):310–320. [PubMed: 20151456]
25. Li L, et al. GL-V9, a newly synthetic flavonoid derivative, induces mitochondrial-mediated apoptosis and G2/M cell cycle arrest in human hepatocellular carcinoma HepG2 cells. *Eur J Pharmacol.* 2011; 670(1):13–21. [PubMed: 21944925]
26. Lu Y, et al. Procyanidins from grape seeds protect against phorbol ester-induced oxidative cellular and genotoxic damage. *Acta Pharmacol Sin.* 2004; 25(8):1083–1089. [PubMed: 15301744]
27. Pajuelo D, et al. Chronic dietary supplementation of proanthocyanidins corrects the mitochondrial dysfunction of brown adipose tissue caused by diet-induced obesity in Wistar rats. *British Journal of Nutrition.* 2011:170–178. [PubMed: 21733324]
28. Cheng M, et al. Cardioprotective effects of grape seed proanthocyanidins extracts in streptozocin induced diabetic rats. *J Cardiovasc Pharmacol.* 2007; 50(5):503–509. [PubMed: 18030059]
29. Yokozawa T, Kim HJ, Cho EJ. Gravinol ameliorates high-fructose-induced metabolic syndrome through regulation of lipid metabolism and proinflammatory state in rats. *J Agric Food Chem.* 2008; 56(13):5026–5032. [PubMed: 18540612]
30. Milczarek R, Klimek J, Zelewski L. The effects of ascorbate and alpha-tocopherol on the NADPH-dependent lipid peroxidation in human placental mitochondria. *Mol Cell Biochem.* 2000; 210(1–2):65–73. [PubMed: 10976759]
31. Gohil K, et al. Vitamin E deficiency and vitamin C supplements: exercise and mitochondrial oxidation. *J Appl Physiol.* 1986; 60(6):1986–1991. [PubMed: 3722064]

32. Nehra D, et al. Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids. *Aging Cell*. 2012; 11(6):1046–1054. [PubMed: 22978268]

TABLE 1

Dietary Interventions Potentially Relevant For Targeting Mitochondrial Function For Fertility Enhancement.

Nutrient	Experimental setting	Specific aspect of mitochondria biology impacted	REF
Carnitine	Boar sperm	Improved sperm quality, morphology	[19]
	Human sperm and serum	Improved sperm motility, decreased oxidative stress	[20], [21]
	Blood and sperm of patients with epididymitis	Reduced reactive oxygen species, increased sperm viability, increased spontaneous pregnancy	[22]
Coenzyme Q10	Oocytes of mice receiving ovarian stimulation	Improved oocyte mitochondrial activity	[23]
N-acetylcysteine	Human luteal cells	Impaired mitochondrial metabolism and cell survival	[24]
Proanthocyanidins	Human endothelial cells	Protection from apoptosis after exposure to advanced glycation end products, a diabetic model	[25]
	Mouse fibroblasts	Decreased oxidative stress after toxic exposure	[26]
	Adipose tissue of rats with diet-induced obesity	Protection from weight gain, enhancement of brown adipose tissue mitochondrial function, decreased triglycerides and increased oxidative capacity	[27]
	Skeletal muscle of a rat model of genetic obesity	Improved muscle mitochondrial function, decreased reactive oxygen species production	[11]
	Myocardium and blood of diabetic mice	Fewer advanced glycation end products, inflammatory cytokines, decreased mitochondria degeneration	[28]
	Metabolic markers of rats with fructose-induced metabolic syndrome	Lowered serum glucose, total cholesterol, blood pressure and triglycerides, decreased inflammatory markers	[29]
Vitamin E	Human placental mitochondria	Decreased lipid peroxidation	[30]
	Adipose and connective tissue of vitamin E deficient rats	Decreased mitochondrial activity in brown adipose tissue, decreased endurance capacity	[31]
Omega-3 Fatty Acids	Mouse Oocytes	Decreased mitochondrial aggregation in oocytes and improved oocyte quality with advanced maternal age	[32]