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Review Article

Therapeutic Roles and Safety Profiles of Non-Vitamin Antioxidant Supplements in Female Infertility: A Narrative Review

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Abstract

Objective: Treatment of female infertility consists different strategies including metabolic, hormonal and surgical therapeutic modalities. Non-vitamin supplements with antioxidant activity as carnitines, Inositols, Poly Unsaturated Fatty Acids (PUFAs), coenzyme Q10 and melatonin are among those with most popularity, but their prescription may confer some warnings.

Materials and methods: This review narrates the antioxidant mechanism of these supplements, beside their effect on outcomes of infertility treatment while considering side effects, warnings and ranges of doses.

Results: Carnitines are used for energy production and fat metabolism, while they have anti-aging and antioxidant effects. Supplementation with carnitines improve obesity outcomes, especially in Poly Cystic Ovarian Disease (PCOS) patients. Rare cases have shown increasing risk of seizure with levocarnitine. Coenzyme Q10 (Ubiquinone) has shown benefit in patients with PCOS or poor ovarian responders. It significantly increased live birth rate and the side effects are minimal even in higher doses. Poly Unsaturated Fatty Acids (PUFAs) have shown impact on follicular development and embryo quality. The hazard is increasing lipid low density lipoprotein (LDL) in high doses. Use of inositols in female infertility treatment is due to its metabolic effect and insulin resistance in PCOS patients resulting in decreasing use of gonadotropins. They have produced acceptable results about count of follicles and oocyte quality. Hypoglycemic effects of inositols have been reported as side effect, especially in combination with other hypoglycemic agents. Melatonin can increase the clinical pregnancy rate, and improve the outcomes about oocyte and quality of embryo via receptor- and non-receptor- action. Dizziness, drowsiness, and headache are reported in higher doses of melatonin.

Conclusion: The attitude that all supplement can be prescribed without restriction endangers susceptible patients. Hence, increasing our knowledge about efficacy and safety profile can help individualize prescription of supplements for female infertility.

Keywords: Antioxidant; Female Infertility; Oxidative Damage; Drug Safety

Introduction

Female infertility is a multifaceted condition that encompasses a broad spectrum of metabolic, obstetric, physiological deficiencies, and congenital disorders (1, 2). While hormonal interventions including ovulation induction, superovulation and procedural methods i.e. assisted reproductive technology (ART)

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are mainstay of the therapeutics, supplements and alternative medicine are adjunctive therapies that are being prescribed for many years (3, 4).

Antioxidant activity is one of the major properties that has been applied to select specific ingredients for adjunctive infertility treatment (5). Sometimes finding a special ingredient in the fluid surrounding the oocyte was proof of its role in fertility mechanisms (like melatonin) (5). However, most of the supplements had demonstrated antioxidant activity in their cellular mechanism before they were introduced to infertility studies (6). These supplements, regardless of the route they have taken into fertility studies, should be the subject of more comprehensive scrutiny.

Vitamins are among the most inspected antioxidant elements in infertility investigations and they are prescribed regularly in various therapeutic forms (7). Non-vitamin supplements with antioxidant activity as carnitines, Inositols, Poly Unsaturated Fatty Acids (PUFAs), coenzyme Q10 and melatonin have also been assessed in different aspects of infertility, but their prescription may confer some warnings (8). While most attentions have regarded efficacy of such supplements, data about safety profile in infertility field is scarce.

The emphasis on non-vitamin supplements is due to several key factors. Unlike vitamins, which are generally included in the medication regimens of infertile patients and have a well-established safety profile, non-vitamin antioxidants are less frequently studied and prescribed. Furthermore, because their side effects and potential interactions require more careful consideration, this class of supplements warrants a more focused discussion. In this narrative review, we discussed a broader vision of non-vitamin supplements from efficacy in different outcomes of infertility (like number of oocytes, number of matured follicles, etc.) to their safety profile and warnings that should be taken into account at the time of prescription. The focus is mostly on non-vitamin supplements with antioxidant activity.

Carnitines

Carnitine is naturally synthesized from the amino acids methionine and lysine and serves as a key cofactor in the transport of fatty acids into mitochondria for subsequent β-oxidation (9). The most common form, L-carnitine (LC), facilitates the transfer of acyl groups to form acyl-CoA, which serves as a substrate for energy production (10). Additionally, LC acts as an antioxidant by scavenging reactive oxygen species, thereby reducing oxidative stress within cells (11). Consequently, LC is recognized both as a metabolic supplement and an antioxidant (12). Acetyl L-carnitine (ALC) is the acetylated ester form of LC that donates an acetyl group to assist in the transfer of fatty acids to mitochondria and possesses neuronal activity (11). Carnitines contribute to cell membrane stabilization through acetylation of phospholipids and amphiphilic properties (9). Although LC and ALC exhibit slight differences in their mechanisms, both are utilized in infertility treatments: LC primarily for energy production and fat metabolism, and ALC for its anti-aging and antioxidant effects (13). Nonetheless, both forms share overlapping activities.

Earlier studies suggest the use of carnitines in PCOS (Poly Cystic Ovarian Syndrome) patients. Since PCOS is a complex of endocrine disorders like insulin resistance, obesity, and hormonal imbalance, supplementation with carnitines can help different dimensions of this endocrinopathy. Some evidence showed supplementation with carnitines can decrease BMI (Body Mass Index), reduce weight and waist/hip circumferences, and enhance serum sugar control in PCOS patients (14). Another study revealed that non-obese patients with a diagnosis of PCOS had a low reservoir of LC, resulting in higher androgen levels and insulin resistance (15). Additionally, carnitine supplementation leads to better results for the development of follicles, even in clomiphene-resistant and gonadotropin-resistant patients (16, 17). The latest meta-analysis showed that LC supplementation in PCOS patients can result in better chemical and clinical pregnancy, better ovulation rate, higher progesterone level, higher number of mature follicles, and better endometrial thickness (18). About estrogen level, dose-response analysis showed that longer duration of LC supplementation can improve serum estrogen level (19). Other studies showed that ALC has additional advantages for Functional Hypothalamic Amenorrhea (FHA) through a neuroprotective effect and acting on hypothalamic-hypophyseal-gonadal axis (20).

The Dosing range of ALC and LC is from 250 mg/d to 4 g/d. But the usual doses used in female infertility is between 2-3 g/d (21). Levocarnitine has an acceptable safety profile. Although rare cases have reported increasing risk of seizure with levocarnitine, studies have shown that the warning is not serious (22). However, this has been noted in levocarnitine monograph.

Coenzyme Q 10

Ubiquinone or Coenzyme Q10 is a lipid-soluble molecule and has a key role in oxidative phosphorylation of the inner mitochondrial membrane (23). Coenzyme Q10 exists in three forms: fully oxidized form, semiquinone intermediate, and fully reduced form (24). That's how it transfers high-energy electrons into inner mitochondrial membrane and establishes a H+ transmembrane gradient (23). Such a gradient is necessary for the production of ATP. It also helps in the regeneration of alpha-tocopherol and ascorbic acid, thus reducing oxidative stress damage (25).

Most of the studies that reported the addition of coenzyme Q10 to the infertility drug schedule used it for PCOS or POR (Poor Ovarian Response) patients. In PCOS patients. It was revealed that coenzyme Q10 improves insulin resistance, fasting insulin, fasting plasma glucose, increase sex hormones, and decrease blood lipids (26). Another meta-analysis has shown that administration of coenzyme Q10 can significantly improve clinical pregnancy rate. But it didn't affect live birth rate, while it had no effect on miscarriage rate (27).

The dosage of Coenzyme Q10 was different through female infertility studies. in POR patients the dosage was among 200 mg three times daily to 600 mg twice daily (28). In PCOS patients, the dosage used were mostly 60 mg three times daily (26). The precaution of coenzyme Q10 is negligible and two studies that has monitored side effects report none. Even at the doses of 900 mg/day, no adverse effect has been reported (29).

Polyunsaturated Fatty Acids

Poly Unsaturated Fatty Acids (PUFAs) are sources of energy in the body and have functions in blood pressure regulation, cell membrane structure, and protection of the cardiovascular system (30). Among these fatty acids, omega-3 fatty acids ranks as higher due to their various anti-inflammatory, vasodilatory, bronchodilatory, and platelet anti aggregatory effect (31). Besides antioxidative action, omega-3 has protective action against metabolic and chronic diseases (32). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the main components of omega-3 fatty acids. As most of these fatty acids are found in fish and marine foods, taking omega-3 is mostly related to lifestyle and dietary habits (33).

It is supposed that the concentration of omega-3 in the follicular fluid surrounding oocyte is a direct consequent of daily omega-3 intake (34). High quantity of lipids is accommodated around oocyte, so they can serve as main source of ATP by oxidation (34). It seems that the profile of lipids around oocyte is prominent for oocyte development, so lack of a good energy source can result in infertility (35).

Most of the investigations that have assessed omega-3 fatty acids as dietary supplements have shown that it has positive effects on follicular development and embryo quality (36). But most of them are not randomized clinical trials, though with low quality of evidence (36). However, the latest meta-analysis revealed that supplementation with omega-3 can increase the clinical pregnancy rate both in patients who conceived naturally and who were under ART treatment (37). The interesting result is that enrichment of the diet with omega-3 fatty acids would prevent ovarian aging and improve oocyte quality, while omega-6 fatty acids, even in short-term will result in poor oocyte quality (37). That's why it should be taken into consideration not to recommend combination of PUFA and only recommend omega-3.

Some of the studies have included omega-3 fatty acids in the diet as lifestyle modification, so the correct dose is not clear (38). But the investigations that have used pharmaceutical forms, applied 1000-2000 mg omega-3, containing DHA and EPA. The most prominent precaution for PUFA is an increasing in LDL levels. However, this effect is a consequence of high doses of omega-3 fatty acids, and the doses that are used in infertility setting is much lower.

Inositols (Myoinositol and D-Chiroinositol)

Inositols are a combination of nine stereoisomers that two of which include myoinositiol and D-chiro-inositol, mediate the post receptor effect of insulin (39). Inositols are mostly found in plant-derived food preparations (40). Uptake free inositol is done by membrane-dependent sodium-inositol cotransporter. Myoinositol and d-chiro-inositol are mediated by inositophosphoglycan (IPG), a second messenger. The one that delivers d-chiro is IPG-P and the one attached to myoinositol IPG-A (41). IPG-P activates glycogen synthesis. IPG-A causes direct glucose uptake and inhibit cyclic AMP protein kinase A, and adenylate cyclase. The result of the mechanism of both IPGs is activating phosphoprotein phosphatase-1 (41). These effects mimics insulin effect and decrease blood sugar levels, regardless of insulin pathway. In patients with PCOS, the metabolism of inositol and/or glycosylphosphatidylinositol is impaired, contributing to insulin resistance (41). Additionally,

obesity has abnormal IPG-P production independently of PCOS (42).

Most of the therapeutic effects of myo-inositol in ART are related to metabolic aspects and insulin resistance, especially in PCOS patients. Although old studies believed that it may affect fasting blood sugar (FBS), new investigations showed that LH, LH/FSH ratio, and fasting serum insulin significantly decreased, but there was no effect on FBS (43). In infertile women undergoing ART procedures, enhancing PCOS patients' ovaries sensitivity to gonadotropin led to a decrease in the dose of follitropins, alongside a decrease in estradiol levels during ovarian trigger therapy (42, 44). This achievement of decreased requirements for FSH was considered unique due to the reduced risk of OHSS, and it was repeated in other studies as well, with the estimated percentage of decrease being 16 percent (45, 46).

Myo-inositols decrease intermediate size follicles, increase large size follicles, and count of follicles, and improve oocyte quality and maturation (42, 45, 46). Also, it was shown that the total number of retrieved oocytes was not affected by myo-inositol treatment (45, 47). A clinical trial revealed that fertilization rate, oocyte metaphase II, and embryo quality were improved (47). Meta-analysis showed that the clinical pregnancy rate was improved (42, 45, 46). However, antral follicle count and anti-Mullerian hormone was decreased significantly in recent meta-analysis, although the studies were small and heterogenous. Recent meta-analysis showed that average number of retrieved oocytes was not different. Although increasing age and BMI can diminish the effect of myoinositol on number of oocytes. Live birth rate was statistically increased as 1.24 time higher than the placebo group in recent meta-analysis (46).

Most of the studies have used myo-inositol with d-chiro-inositol, and the average dose was 2000-4000 mg per day (48). The duration was mostly 16-24 weeks. However, some studies have reported using myo-inositol for less than two months (49). Myo-inositol may cause diarrhea, flatus, and nausea in patients. Besides, the coadministration of myo-inositol with blood glucose-lowering agents (like metformin) may intensify their effect.

Melatonin

Melatonin has been known both as a regulator for circadian rhythm and antioxidant activity. Although it is mainly secreted from pineal glands, it is also derived from other sites like the retina, bone marrow, gastrointestinal tract, and ovaries (50). Melatonin can downregulate GnRH gene expression in a cyclic manner, thereby affecting LH and FSH secretion (51). Melatonin mitigates oxidative stress in granulosa cells and inhibits autophagy via modulation of signaling pathways such as PI3K–Akt–mTOR (52). That's why it is believed that melatonin can help ovarian aging.

The interesting fact about the antioxidant effect of melatonin is that it exerts its effect through both receptor-mediated and non-receptor-mediated activity (53). It can enter the plasma wall through penetration and act as an antioxidant, while it does not switch between oxidized and non-oxidized forms, because when melatonin performs its antioxidant action, it does not convert to its original form of molecules. Receptor-mediated actions are carried out through MT1 and MT2 receptors that are centrally concentrated in the brain but are found in many other tissues (54).

Melatonin has shown efficacy in various stages of ART. Investigations revealed that melatonin can increase the clinical pregnancy rate, the number of oocytes collected, the number of matured oocytes, and the number of good quality embryos, but it has no effect on the live birth rate (55, 56). The applied dose was 3 mg, and most of the studies have reported clinically significant outcomes in doses below 3 mg. However, doses above 3 mg yielded mixed results (57). The most important side effects of melatonin are drowsiness, dizziness, and headache that is mostly reported in higher doses (up to 30 mg daily).

Table 1 describes the summary of the effects of non-vitamin supplements on outcomes of infertility treatment. In addition, main precaution of each supplement has been mentioned in this summarized table.

Other antioxidants

Some other antioxidants may have therapeutic effects as adjunctive to pharmacotherapy of infertility. Resveratrol is a polyphenolic compound that is found in berries, foods and red wine. It shows anti-inflammatory, tumor-protective, antiaging and antioxidant activity (58). It has been used in infertility treatment for improving ovarian function and prevent ovaries from aging especially in PCOS patients (58). Resveratrol increased follicle output rate and follicle to oocyte index in a significant manner (59). Resveratrol may cause gastrointestinal side effects (60).

N-Acetyl Cysteine (NAC) is the acetylated precursor of amino acid L-cysteine and reduced glutathione.

Table 1: Summary effects, range of doses, and safety profiles of antioxidant supplements in infertility treatment (Part I)

Supplements	Improvement of sex hormones	Ovulation	No. of retrieved oocyte	Oocyte quality	Endometrial Thickness	No. of high-quality embryo	Biochemical pregnancy	Clinical Pregnancy rate	Live birth rate
Carnitines	✓	✓	✓	-	✓	-	✓	✓	-
Coenzyme Q10	✓	-	-	-	-	✓ or ×	-	✓	×
PUFA	-	✓	-	✓	-	-	-	✓	-
Myoinositols	-	-	✓ or ×	✓	-	✓	-	✓	✓
Melatonin	-	-	✓	✓	-	✓	-	✓	×

Table 1: Summary effects, range of doses, and safety profiles of antioxidant supplements in infertility treatment (Part II)

Supplements	Dosage	Adverse effects*	Precautions for infertile women	Main reference
Carnitines	250 mg/d to 4 g/d, mostly in two divided doses	Cardiovascular side effects (atrial fibrillation, ECG changes, chest pain), abdominal cramps, abdominal pain, diarrhea, nausea, vomiting, dizziness, headache, vertigo, paresthesia, bronchitis, cough, fever	Rare reports of seizure, Gastrointestinal effects,	(18)
Coenzyme Q10	200 mg TDS to 600 mg BD	Stomach upset, anorexia, nausea, diarrhea, skin rash	None	(27)
PUFA	1000-2000 mg omega-3 daily	Dysgeusia, dyspepsia, eructation, constipation, vomiting, pruritus,	Increasing LDL in high doses, increase in miscarriage rate in high exposure to Omega-6, bleeding in concomitant use with antiplatelet and anticoagulants agents, fish allergy, increase in hepatic enzymes, increased LDL cholesterol	(37, 67)
Myoinositols	2000-4000 mg per day	Diarrhea, cramp and nausea	Decrease in blood sugar	(45-47)
Melatonin	3 to 9 mg every night	Drowsiness, headache, dizziness, loss of appetite, diarrhea, nausea, vivid dreams, nightmare, depression, irritability,	Autoimmune conditions (melatonin is an immune booster), changes in blood pressure, seizure, dementia, use of sedatives	(55)

✓ Indicates that the attributed supplement can significantly affect the outcome
× Indicates that the attributed supplement didn't significantly affect the outcome
- Indicates that the data is not enough about effect of the supplement on such outcome
TDS means three times daily. BD is indicated for two times daily.
*The frequency of side effects of supplements is not defined clearly. But the effort was put to give a complete safety profile in this table.

The antioxidant activity of NAC is well recognized through inhibition of cell apoptosis and improving cell survival (61). The latest meta-analysis has revealed that NAC can enhance profile of sex hormones in PCOS patients i.e. decreasing testosterone level and increasing estrogen and FSH level (62). Adverse effects of NAC consists of upset stomach, metallic taste, lightheadedness, sleepiness (63).

Alpha lipoic acid (ALA) is a potent antioxidant that shows radical scavengering activities (64). Although most of the studies about ALA and infertility are focused on male factors, some investigations have depicted improving metabolic parameters in patients with diagnosis of PCOS (65). ALA has an acceptable safety profile and only rare report of increasing liver enzyme has been observed in high doses in animal studies (66).

Conclusion

Non-vitamin supplements have been widely prescribed for treatment of infertility. While their unique indication beyond antioxidant activity should be considered for prescription (like decreasing the requirement for gonadotropins in prescribing inositols, or improving metabolic parameters in obese patients with carnitines) their overall antioxidant activity is desired. Increasing our knowledge about safety considerations of each supplement can help in individualizing treatment for susceptible patients.

Conflict of Interests

Authors declare no conflict of interests.

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