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ALFA-LIPOIC ACID IN OBSTETRICS AND GYNECOLOGY

Alpha lipoic acid in obstetrics and gynecology

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ABSTRACT

Alpha-Lipoic acid (ALA) is a natural antioxidant synthetized by plants and animals, identified as a catalytic agent for oxidative decarboxylation of pyruvate and α-ketoglutarate. In this review, we analyzed the action of ALA in gynecology and obstetrics focusing in particular on neuropathic pain and antioxidant and anti-inflammatory action. A comprehensive literature search was performed in PubMed and Cochrane Library for retrieving articles in English language on the antioxidant and anti-inflammatory effects of ALA in gynecological and obstetrical conditions. ALA reduces oxidative stress and insulin resistance in women with polycystic ovary syndrome (PCOS). The association of N-acetyl cysteine (NAC), alpha-lipoic acid (ALA), and bromelain (Br) is used for prevention and treatment of endometriosis. In association with omega-3 polyunsaturated fatty acids (n-3 PUFAs) with amitriptyline is used for treatment of vestibulodynia/painful bladder syndrome (VBD/PBS). A promising area of research is ALA supplementation in patients with threatened miscarriage to improve the subchorionic hematoma resorption. Furthermore, ALA could be used in prevention of diabetic embryopathy and premature rupture of fetal membranes induced by inflammation. In conclusion, ALA can be safely used for treatment of neuropatic pain and as a dietary support during pregnancy.

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Introduction

Alpha-lipoic acid (ALA) is a natural antioxidant lipophilic compound which acts as an essential cofactor for mitochondrial enzymes. It increases the effectiveness of other antioxidants as glutathione by 30–70%, especially in liver, lung and kidney cell cultures in a laboratory [1,2]. The complex ALA-DHLA intervenes in the repair of proteins lipids and DNA damaged by oxidation [3]. ALA has been used in patients with type-2 diabetes to improve glycemic control and to reduce symptoms of diabetic neuropathy and has gained attention in the last years for the treatment of liver and neurological diseases.

In this review, we analyzed the action of ALA in gynecology and obstetrics focusing on its antioxidant and anti-inflammatory action.

Alpha-lipoic acid in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) affects 4% to 12% of reproductive age women and is characterized by hyperandrogenemia, amenorrhea and anovulation [4].

Recent evidence shows that oxidative stress is increased in PCOS women because of an increased production of free radicals followed by decreased serum antioxidant levels and antioxidant enzyme activity. The increased oxidant status appears to worsen the insulin resistance state [5].

ALA plays a role in the regulation of glucose and lipid metabolism by stimulating glucose uptake with an intracellular redistribution of GLUT1 and GLUT4 glucose transporters, similar to that caused by insulin [6].

Growing evidence suggests that alpha lipoic acid may improve reproductive function and metabolic parameters in women affected by PCOS.

One recent study assessed the efficacy of a combination of 400 mg of alpha lipoic acid and 1 g of myo-inositol in reducing insulin resistance and glucose-load induced hyperinsulinemia in a group of 36 PCOS patients, improving also gonadotropin secretion. All the patients had a significant reduction of LH serum levels and LH/FSH ratio, however only hyperinsulinemic PCOS patients did show variations in Homeostasis Model Assessment Insulin Resistance index (HOMA-IR) and response to oral glucose tolerance test (OGTT) that indicated a significant increase in isulin sensitivity [7].

Alpha lipoic acid plus myo-inositol, in addition to treatment with metformin 1.7 g, also showed a better response in terms of hyperandrogenism, BMI and HOMA index than metformin 3 g alone in women with PCOS [8].

Rago et al. evaluated the effects of a cycle of treatment 2 g of myo-inositol and 800 mg of ALA per die in a group of 37 nonobese PCOS patients who had undergone ICSI and did not obtain a pregnancy. After 3 months of treatment, significant effects in insulin levels, BMI and ovarian volume were obsereved, although the pregnancy rate and the oocytes quality were similar to patients who assumed myo-inositol alone [9].

In another recent study, 30 young women affected by PCOS with insulin resistance were treated either with an association of 1 g myo-inositol, 5 mg monacolin K and 400 mg lipoic acid for 6 months or a double dosage of 2 g myo-inositol, 10 mg monacolin K, 800 mg lipoic acid for 6 months. When combined with monacolin K, a natural statin, the treatment with myo-inositol and

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ALA showed a dose-dependent improvement in BMI, dyslipidemia and hyperandrogenism-associated symptoms like hirsutism and menstrual disorders [10]. Treatment with a combination of 1 g D-chiro-inositol (DCI) and 600 mg ALA daily for 180 days versus no treatment in a group of forty-six women (26 study group subjects and 20 controls) of reproductive age with PCOS led to similar results in terms of clinical and metabolic features. In fact, in the study group HOMA-IR, insulin levels, lipid profile and frequency of menstrual cycles were significantly improved [5]. Masharani et al. administrated a preparation of controlled-release ALA 600 mg twice a day for 16 weeks in a group of 6 lean women affected by PCOS. Despite the absence of severe insulin resistance in this group of patients, a therapy with controlled-release ALA led to a lowering of triglyceride levels, improvement in insulin sensitivity and menstrual frequency [4]. Genazzani et al in a recent study describe the improving in metabolic impairment in obese PCOS women especially with a history of familiar diabetes with daily 400 mg of ALA oral assumption. Practically ALA administration improved insulin sensitivity, especially in those patients with diabetic relatives with a defect in function and/or mitochondrial LASY (lipoic acid synthase) synthesis. It is interesting to note that a decrease of triglyceride and GOT plasma levels greatly improved and/or protected liver function in these patients, reducing the risk to develop a liver impairment [11].

Use of alpha-lipoic acid to improve outcome in infertility

In vitro follicular development and maturation are affected by many factors and oxidative stress (OS) seems to have a pivotal role [12].

Under physiological conditions, generation of reactive oxygen species (ROS) occurs during various cellular metabolic reactions, which are equilibrated by antioxidant defense systems. In the *in vitro* setup, higher oxygen levels and lack of physiological defense mechanisms against ROS result in OS [13]. Also, it has been shown that, OS can be induced during assisted reproductive technique procedure by manipulation of gametes and embryos [14].

Talebi et al investigated the effect of ALA on culture mouse isolating preantral follicles. ALA (100uM) increased follicular total antioxidant capacity (TAC) levels, decreased ROS levels, and finally improved the developmental competence of preantral follicles *in vitro*. In the presence of 100 uM ALA, developmental rates of follicles, oocytes and embryos were significantly higher than other groups ($p < .05$) [15]. Zavereh et al confirmed that ALA decreased ROS and increased TAC but could not affect maturation rate of both cumulus oocyte complexes (COCs) and denuded oocytes (DOs) in one or two step *in vitro* maturation manner [16].

In one study performed by Avci et al. [17], the effect of ALA and alfa-tocopherol (ATF), in preventing the toxic effect induced by the exposure to Bisphenol A (BPA) – a commonly used material in daily life which it is argued to cause oxidative stress in and ovarian tissue – was studied.

Apart from their endocrine disrupting effect, studies have shown that they cause cellular damage to protein and lipid structures through ROS in the tissues where BPA accumulates [18]. The administration of ALA (100 mg/kg/day) and ATF (20 mg/kg/day) to female rats for 30 days prevented lipid peroxidation in the liver and ovaries of female rats caused by the administration of BPA.

Furthermore, aging and age-related pathologies are frequently associated with loss of mitochondrial function mainly due to the accumulation of mtDNA mutations and deletions. In oocytes, low levels of mitochondrial oxidative phosphorylation may occur for up to 40 years before follicle maturation and ovulation, further increasing the risk for mtDNA mutations. The result is the increased rate of aneuploidy, especially trisomies, observed in the offspring of older women. It also appears that oxidative phosphorylation and ATP production in the follicle is impaired in older women. It has been demonstrated that embryo implantation potential is correlated with the ATP content of the embryo [19]. Preliminary data demonstrated that CoQ10 treatment, but not ALA and resveratrol, was associated with increased oocyte numbers and oocyte mitochondrial activity parameters, similar to oocytes from young ICR controls [20]. On the contrary to ALA administration alone, the combination of ALA and inositols not only modulate insulin plasma levels but also, thanks to inositols, improved the reproductive pathways thanks to an effect on FSH signal transduction [7,11].

The role of alpha-lipoic acid in treatment of endometriosis and vestibulodynia

Oxidative stress has been suggested in the etiology of chronic pelvic pain [21]. 40–87% of women with chronic pelvic pain have endometriosis [22]. Two studies [23,24] evaluated antioxidant substances, among which the alpha lipoic acid, for the treatment of endometriosis.

Agostins et al., tested the association of 1000 µg/mLN-Acetyl Cysteine (NAC), 500 µg/mL ALA, and 50 µg/mL bromelain for the treatment of endometriosis *in vivo* murine model and *in vitro* model. They evaluated the compound mixture on SCID mice whose peritoneal cavity was injected with human endometriotic tissue. Treated mice grew a significant lower number of cyst compared to untreated animals and larger cysts were observed in untreated animals. They compared the expression of vascular cell adhesion molecule-1 (VCAM1), that plays a critical role in regulation of inflammatory process, on Endometriotic Endothelial cells (EEC) untreated, stimulated for 12 h with TNF-α, and treated withTNF-α previously preincubated for 72 h with NAC, ALA and Br, used alone or in association. They found a significant decrease of VCAM1 levels only with the drug combination. Finally, the authors observed that the NAC/LA/Br mixture was able to induce a statistical significant ($p < .05$) increase of apoptosis of EECs. In conclusion, the NAC/ALA/Br association may have potential therapeutic uses in the prevention and treatment of patients with endometriosis [23].

Caruso et al. assessed the effect of the combination between 300 mg Palmitoylethanolamide (PEA) and 300 mg ALA on quality of life (QoL) and sexual function in 56 women with chronic pelvic pain associated with endometriosis. They studied the intensity of pelvic pain and evaluated QoL and the quality of sexual activity. They did not find significant differences in QoL and sexual activity during the first three months of treatment at the 6th and 9th month of drug assumption, reduction of chronic pelvic pain, dysmenorrhea and dyspareunia was significant, as well as the improvement in all categories of QoL and the sexual function scores [24].

Finally one study evaluated the role of ALA plus omega-3 polyunsaturated fatty acids (n-3 PUFAs) in combination with amitriptyline therapy in patients with vestibulodynia/painful bladder syndrome (VBD/PBS). Eighty-four women were randomly assigned to receive amitriptyline or amitriptyline plus LA

600 mg plus docosahexaenoic acid 250 mg and eicosapentaenoic acid 16.67 mg for 12 weeks. After treatment, the reduction of pain rating index and of the dyspareunia grade was of greater statistical significance in the amitriptyline plus LA and n-3 PUFAs group [25].

Painful bladder syndrome and alpha lipoic acid

Interstitial cystitis (IC) is a chronic syndrome characterized by symptoms of urinary urgency/frequency, pelvic pain, and nycturia in the absence of bacterial infection or any other identifiable pathology [26]. Oral tricyclic antidepressants are commonly used in the treatment of vulvar pain and painful bladder syndrome (PBS)/IC, with amitriptyline used as a first-line agent. Murina et al found out that the addition of ALA/n-3 PUFAs to amitriptyline treatment in patients with painful bladder syndrome (PBS) appears to improve outcomes and may allow for a lower dosage of amitriptyline, which may lead to fewer adverse effects [25].

It has been observed that the urothelial expression of the chemokine fractalkine (CX3CL1) and its receptor (CX3CR1) is markedly increased in a mouse model of chronic cystitis [27]. In this regard, Yuridullah et al. demonstrated a robust upregulation of both CXCL1 and CXCR1 in the urothelium following chronic cyclophosphamide (CYP)-induced cystitis in the rat [27]. Because CYP-induced cystitis closely resembles the features of interstitial cystitis in humans [28], these observations establish downregulation of fractalkine as a potential target for the therapy of this common clinical entity. ALA has been demonstrated to act as an effective agent to reduce fractalkine mRNA and protein expression as well as fractalkine-mediated inflammatory processes [29]; secondly, ALA has the capacity to inhibit TNFa-induced expression of fractalkine [30]. ALA could reverse the harmful effects of high levels of oxidative stress in bladder inflamed tissue due to its potent antioxidant activity [31]. Altogether these observations suggest that ALA may represent a novel pharmacotherapeutic strategy in the clinical management of interstitial cystitis.

Alpha-lipoic acid and miscarriage

Threatened miscarriage is a clinical pregnancy condiction that occurs during the first 20 weeks in almost 20% of gestation. Subchorionic hematoma is the cause of vaginal bleeding in 18% of cases and may increase the risk of pregnancy loss in 46% by immune and inflammatory condition [32,33]. Many cytokins are involved in pathogenic mechanism of miscarriage. In humans many clinical trials were performed to analyze the efficacy and tolerability of ALA in pregnant women. Costantino et al confirmed the safety of the administration of 1200 mg once a day i.v. or 600 mg once a day i.v. for 3 weeks followed by 600 mg three times a day orally for 6 months in pregnant women [34].

The recent use of ALA in patients with threatened miscarriage to improve the subchorionic hematoma resorption is a promising area of researches and studies. During abortion, there is an elevation of TNFα IL2, TNFβ and IFγ induced by TH1 and also an increase of pro inflammatory IL6 secreted by TH2.

Monastra et al in their work evaluated the action of ALA in preventing miscarriage. ALA reduces pro-inflammatory cytokine levels, such as TNF-α, IL-1β, IL-6, IL-8, IL-17 and INFγ, while it induces anti-inflammatory IL-10 release. Other molecules may be involved in the mechanism of subchorionic hematoma resolution. Vascular endothelial growth factor (VEGF) stimulates epithelialization and collagen deposition in wounds and Alpha-Smooth Muscle Actin (alpha-SMA) takes part in fibrogenesis [35–37].

ALA may increase VEGF, as demonstrated in study conducted on rats by Micili et al with enhance of wound healing in uterine full thickness injury. In addition, inflammation is a useful mechanism for the implantation in physiologic pregnancy with an increase of IL-17 released by Th17, but overexpression of IL-17 can harm embryo development. Treg cells instead are involved in the immunoregulation and in the induction of tolerance [38]. ALA suppresses the number of Th17 and increases splenic Treg cells [34,39].

Porcaro et al conducted a randomized controlled clinical trial in pregnant women with threatened miscarriage to test the role of ALA supplementation (600 mg by oral route) in improving the standard treatment with progesterone vaginal suppositories, in healing subchorionic hematomas and also in reducing vaginal bleeding, abdominal pain, and uterine contractions. The group treated with progesterone plus ALA had a better and faster evolution during the first 20 weeks of gestation. Signs of threatened abortion decreased or disappeared in the group treated with ALA plus progesterone, faster than in the group treated with progesterone alone. There was a clinical evolution of uterine wound healing and hematoma resorption in patients treated with ALA [40].

Costantino et al studied the administration of 400 mg of vaginal Progesterone or 10 mg of vaginal ALA in 62 pregnant women, in the first trimester of gestation with threatened miscarriage and subchorionic hematoma. In the ALA group, the subchorionic hematoma was reabsorbed more quickly in comparison with the progression detected in progesterone group. The number of miscarriages was smaller in the ALA group, compared to progesterone group [41].

Alpha-lipoic acid and gestational diabetes

Maternal gestational diabetes (GDM) is known to increase the risk of congenital malformation [42,43]. Some studies evaluated the protective effect of lipoic acid (ALA) on fetal outcome of diabetic mothers. Coughlan et al have studied placental tissue from women with GDM and found out that in response to oxidative stress, TNF alpha, 8-isoprostane release and nuclear factor-KB (NF-KB) DNA- binding activity were significantly increased in normal tissues (20-fold, 2-fold, and 35%, respectively, $p < .01$). Conversely, there was not a significant increase in GDM placental tissues [44]. On the basis of this information, we hypothesize that the antioxidative activity of LA might be effective in preventing diabetic embryopathy. In fact, there have been different reports that suggest the beneficial effect of ALA in preventing diabetic embryopathy in rats [45–47]. In particular Sugimura et al treated daily with either ALA (100 mg/kg body weight) or saline between gestational days 0 and 18 pregnant diabetic or nondiabetic mice. ALA treatment decreased the incidence of cardiovascular malformations (CVMs) from 30 to 3%, of skeletal malformations from 29 to 6%, of external malformations from 39% to 11% and of neural tube defects (NTDs) from 30% to 8% [45]. An *in vitro* study conducted on human umbilical vein endothelial cells (HUVECs) demonstrates that both Centella asiatica (CA) and ALA, or a combination thereof, are able to reduce the inflammatory response induced congenital malformations, therefore, potentially dangerous on the endothelium of chronic exposure to hyperglycemia *in vivo* [48].

Alpha-lipoic acid and premature rupture of fetal membranes

Preterm birth is one of the major cause of neonatal mortality and morbidity [49]. In one third of preterm births the triggering

event is constituted by preterm premature rupture of fetal membranes (pPROM). It is hypothesized that fetal membranes are weakened and ultimately ruptured as a result of collagen remodeling and apoptosis [50,51]. Tissue remodeling has been strongly associated with production of reactive oxygen species (ROS) that induce matrix metalloproteinase 9 (MMP9) and prostaglandins [52]. Antioxidants have therefore been proposed as potential inhibitors of premature fetal membrane remodeling and preterm rupture.

Moore et al., in 2009 [53] observed that ALA inhibits TNF-induced weakening, decreasing MMP9 and PGE 2 release in cultured *in vitro* fetal membranesand TNF and IL1B-induced MMP9 release by cultured amnion epithelial cells.pPROM is highly associated with decidual hemorrhage with resultant thrombin production [54–57].

Moore et al., in 2010 [58] demonstrated that thrombin caused fetal membranes weakness *in vitro* in a dose-dependent manner and induced collagen remodeling in the amnion component of the FM, by induction of MMP9 protein. The incubation of ALA with FM fragments inhibited thrombin-induced FM weakening and abolished the thrombin-induced increases of MMP9 in amnion component.

Kumar et al., in 2011 confirmed that thrombin weakened isolated AM in a dose-dependent manner. Pre-incubation with ALA completely inhibited thrombin-induced AM weakening and inhibited the thrombin-induced increase in MMP9 [59].

Conclusions

ALA is a promising antioxidant in gynecology. The first field of application is the treatment of neuropatic pain and phase three studies demonstrated the role of ALA in the treatment of dismenorrea and vulvar pain.

Studies in patients with PCOS demonstrated an improvement in amenorrhea and hyperandrogenism with beneficial effects on fertility. The use of ALA on infertile patients was not tested in phase three studies and other studies are necessary to assess the role of this agent in the treatment of infertility.

The use of ALA as a dietary supplement during pregnancy has risen greatly in recent years. Various studies were conducted to explore not only its efficacy, but also its safety in the prevention of pPROM and gestational diabetes, although further studies are required to evaluate its tolerability.

With regard to dosage in humans, oral ALA supplementation at doses of up to 2400 mg/day and intravenous administration of 600 mg/day did not seem to have any side effects [60]. These studies were carried out mainly on animals or on small numbers of patients, and this is their major drawback. Similar studies in vivo, with a larger sample size, are necessary to confirm the biological significance of these findings. It is important to focus on another drawback of ALA: its costs. We also noticed that in almost all studies, ALA was always administered in combination with other molecules. Therefore, in our opinion, further studies are needed to evaluate its real benefits.

Disclosure statement

The authors report no conflict of interest.

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