Benefits of α-lipoic acid in high-risk pregnancies (Review)

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Abstract. α-Lipoic acid (ALA) is a natural molecule that is inconsistently synthesized by the human body and must be provided from exogenous sources, such as food and dietary supplements. Once absorbed, the oxidized form of ALA is transformed into its reduced form, dihydrolipoic acid (DHLA). ALA/DHLA exert direct and indirect anti-oxidant, anti-inflammatory and fine immunomodulatory effects. ALA/DHLA reduce the levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and IL-17), while increasing the secretion of anti-inflammatory cytokines (IL-10). They also inhibit cyclooxygenase 2, thereby decreasing the secretion of prostaglandin E2 and nitrogen oxide, and reducing the risk of miscarriage in the first trimester of pregnancy. In patients at risk of abortion, administration of ALA from the first trimester has shown efficacy by accelerating subchorionic hematoma resorption, with a significant decrease in the accompanying abdominal pain. ALA has been proven to be efficient in maintaining the length of the cervix and keeping it closed following one episode of premature labor. Preeclampsia is a dysfunction caused by abnormal placentation and an excessive maternal inflammatory response, leading to extreme hypoxia in the placental bed and exaggerated oxidative stress, with release of oxygen free radicals. Oxidative stress plays a key role in the development of preeclampsia and intrauterine growth restriction. The hypothesis of antioxidant supplementation may play an essential part in disease prevention and fetal neuroprotection.

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1. Introduction

Alpha-lipoic acid (ALA) is an organosulfur compound (chemical formula: $C_8H_{14}O_2S_2$), with a molecular weight of 206.32 Da, which is synthesized by plants, animals, as well as humans (1,2).

Endogenous ALA is synthesized in the mitochondria from octanoic acid. This natural molecule, which is essential for a number of metabolic processes, is inconsistently synthesized by the human body in insufficient quantities. Consequently, ALA must be obtained from exogenous sources, such as food and dietary supplements, with red meat (e.g., liver, heart and kidney) representing a major supply source. Significant quantities of this molecule are also found in vegetables, such as tomatoes, spinach, Brussels sprouts, peas, potatoes, broccoli and brown rice (2). Lipoic acid plays a key role in energy and amino acid metabolism through forming covalent bonds with specific proteins, serving as part of the essential mitochondrial multi-enzyme complexes (2). There is currently a growing scientific and medical interest in the therapeutic use of lipoic acid, and it was lately introduced in pregnancies at risk of miscarriage/premature delivery, or in cases of intrauterine growth restriction (3).

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Once absorbed, the oxidized form of the ALA molecule is transformed by a specific enzymatic mechanism (dihydrolipoamide dehydrogenase, thioredoxin reductase, or glutathione reductase) into its reduced form, dihydrolipoic acid (DHLA) (4). Both forms may be identified in living organisms, exercising a biological function under different circumstances. ALA and DHLA comprise a solid redox couple. Their physical activity is interchangeable and depends on the microenvironmental conditions (the cytoplasm is a reducing medium; thus, ALA is reduced to DHLA after entering the cell) (5).

Pharmacokinetic studies have shown that different doses (50-600 mg) of orally administered ALA are completely absorbed within 30-60 min, with a plasma half-life of 30 min (6). Rapidly metabolized ALA has a bioavailability after the first passage of ~30% (range, 20-38%). ALA is mainly stored in the heart, kidneys and liver (7,8).

Spontaneous abortion in the first 20 weeks of pregnancy, particularly in the first trimester, is a common problem during pregnancy, with the most common causes being genetic abnormalities (5,9), inflammatory processes (10) and immune dysfunction (11). The primary manifestation is vaginal bleeding, which is frequently accompanied by lumbar-abdominal pain and a feeling of pressure in the pelvis. A total of 18% of vaginal bleeding cases in the first trimester develop a subchorionic hematoma. The risk of miscarriage in early pregnancy is 20%, while half of these cases have a subsequent increased risk of premature delivery (12).

The aim of the present review was to discuss the positive effect of ALA administration in high-risk pregnancies. Miscarriage and premature birth share a common pathophysiological pathway, manifested by an imbalance between pro- and anti-inflammatory cytokines. As the ALA molecule has well-known antioxidant, anti-inflammatory and immunomodulatory properties, it may be of value in this setting, and is already being utilized on a limited scale.

2. ALA/DHLA action

Most studies describe that ALA/DHLA exert direct antioxidant, anti-inflammatory and immunomodulatory effects, whereas they may also exert indirect antioxidant effects by contributing to the regeneration of other essential antioxidant molecules, such as coenzyme Q10, vitamin C and vitamin E. ALA/DHLA may also chelate a number of heavy metals implicated in oxidative processes, such as iron, lead, cadmium, mercury, copper and arsenic (5-7,13,14).

Antioxidant activity. Increased generation of oxygen free radicals has been reported to be involved in the pathophysiology of first-trimester miscarriage (15). Serum prolidase activity, sulfhydryl levels and total antioxidant capacity (markers of oxidative stress) have shown statistically significant changes in such cases (16). Patients at risk of abortion exhibit changes in the regulation of oxidase activity of peripheral blood granulocytes (17). Peroxiredoxins are antioxidant proteins expressed by cytotrophoblastic cells, and their downregulation is often associated with miscarriage (15).

The ALA/DHLA redox couple is involved in the repair of biological molecules, such as proteins, lipids and DNA, which are damaged by oxidation. At the protein level, oxidation occurs at the level of amino acids such as methionine, cysteine, histidine, tyrosine and tryptophan. The oxidation of methionine may cause protein inactivation and the alteration or inhibition of their enzymatic, hormonal and/or chemotactic functions. Lipoamide, the neutral amide of ALA, is involved in the repairing process of oxidized methionine (18).

Thus, ALA/DHLA exert antioxidant effects *in vitro* through four different mechanisms (19): i) Elimination of oxidants; ii) regeneration of endogenous antioxidants; iii) chelation of transition metals; and iv) reparative action of oxidative damage.

Some researchers dispute the *in vivo* antioxidant activity of ALA/DHLA, mainly due to the inability to reach a sufficient serum concentration by oral administration to achieve elimination of free radicals (20).

Anti-inflammatory and immunomodulatory action. Recent research has shown that high titers of pro-inflammatory cytokines (IL-1 and IL-6) (14,15,18) and/or low titers of anti-inflammatory cytokines (IL-4 and IL-10) (8) increase the risk of miscarriage and preterm delivery (Fig. 1).

Current studies have described the role of specific cytokines, growth factors, chemokines and helper T cells in the etiopathogenesis of miscarriage and preterm delivery. There are two subsets of CD4$^+$ lymphocytes, namely T helper 1 (Th1) and T helper 2 (Th2) cells, classified according to the type of secreted cytokines (5,21).

Th1 cells predominantly secrete TNF-β, IFN-γ, IL-2, TNF-α and TGF-β. TNF-α protects the fetoplacental unit (22,23), but it is also involved in the immunopathology of various pregnancy complications. TNF-α increases the level of the trophoblast-derived plasminogen activator inhibitor-1 and decreases its invasive capacity (24,25). Th1 cells also secrete IL-10, albeit in small amounts, which is a cytokine with a critical role in controlling inflammation and self-regulating Th1 cell activation (21).

On the other hand, Th2 lymphocytes predominantly secrete IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and TGF-β, and small amounts of TNF-α and IL-2. All these molecules are involved to different extents in the implantation process and the evolution of normal/abnormal placentation (26). In particular, IL-4, which has an anti-inflammatory role, and IL-6, which has a pro-inflammatory role, are involved in modulating the risk of miscarriage (27).

Prins *et al* (28) demonstrated a significant increase in serum IL-6 concentrations in women who had suffered habitual abortion, supporting the pro-inflammatory and pro-abortive role of this cytokine in early pregnancy.

By contrast, IL-4, similar to IL-10, is an anti-inflammatory cytokine with a preventive role in miscarriage. Chatterjee *et al* (29) reported that a decrease in serum IL-4 below average values exerted pro-inflammatory effects and increased the risk of abortion.

Saito *et al* (27) and Kaminski *et al* (30) investigated the role of regulatory T cells (Tregs) and Th17 cells, responsible for the release of IL-17, and their dual action in pregnancy. Th17 cells serve an immune protective role against the maternal microbiome in the uterus (5). Average IL-17 levels determine the normal degree of inflammation that accompanies the oocyte fertilization process in pregnancy (31), whereas elevated IL-17
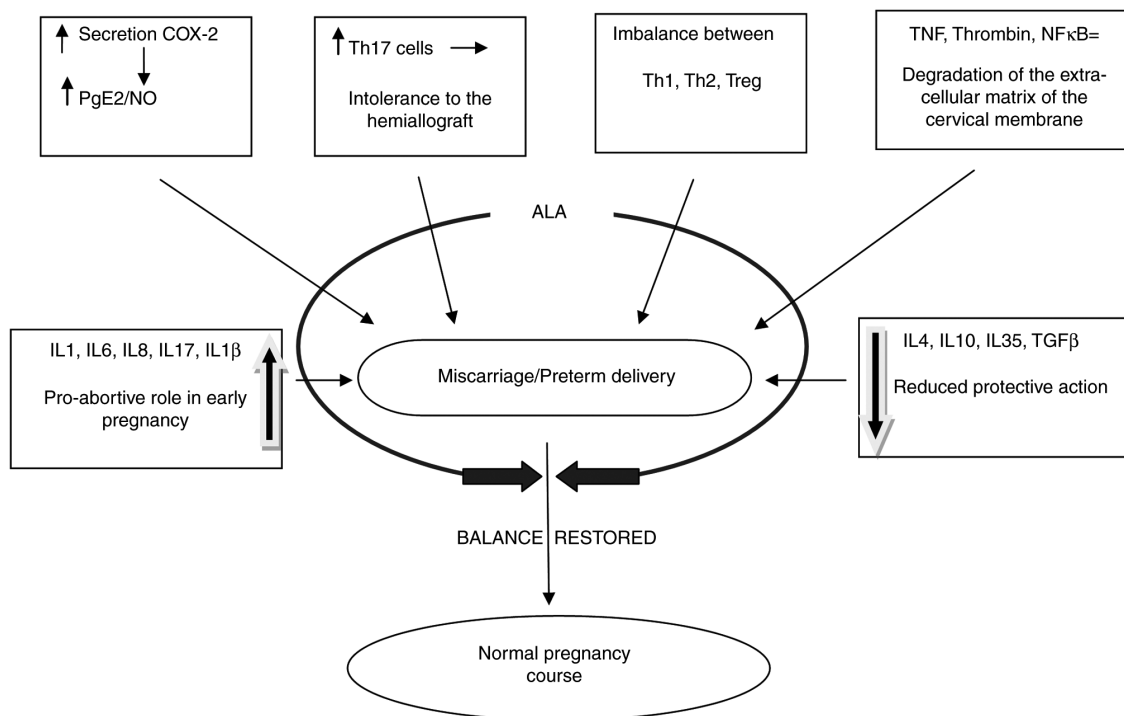
Figure 1. Schematic illustration of the role of specific cytokines, growth factors, chemokines and helper T cells in the etiopathogenesis of miscarriage and preterm delivery. ALA, α-lipoic acid; COX, cyclooxygenase; Pg, prostaglandin; NO, nitric oxide; Th, T helper; Treg, regulatory T cell.

levels explain the excessive pro-inflammatory mechanism underlying spontaneous abortion (32-34).

Tregs and Th1 cells can be converted to Th17 cells (35,36), thus ensuring the fine immunomodulation and tolerance to the fetal hemiallograft. The cells release the anti-inflammatory cytokines TGF-β, IL-10 and IL-35, which directly or indirectly block the secretion and activity of pro-inflammatory cytokines. There is an interdependence between the Treg, Th1 and Th2 cell types and the cytokines released by them in normal pregnancies.

Therefore, a balance between Th1 and Th2-mediated immunity (predominantly Th2) is required to maintain a normal pregnancy (5), without exacerbated secretion of certain cytokines to compensate for the deficiency of others (Fig. 1).

3. ALA impact on high-risk pregnancies

Medication for women at risk of abortion and premature birth must modulate pro and anti-inflammatory cytokines to restore the delicate balance. DHLA, the reduced form of ALA, has demonstrated marked efficacy as a free radical scavenger and modifier of oxidative stress and inflammation-related pathways (37).

Numerous scientific studies have shown that ALA administration may be beneficial in high-risk pregnancies (Table I).

Beneficial effects of ALA on threatened abortion. In patients at risk of spontaneous abortion, ALA administration starting from the first trimester has shown efficacy by accelerating the resorption of subchorionic hematoma, with a significant decrease in the accompanying abdominal pain (38-40). ALA is implicated in fine immunomodulation and interdependence among Tregs, Th1 and Th2 cells.

ALA reduces the levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and IL-17), while it increases the secretion of anti-inflammatory cytokines (IL-10) (5,41). It also inhibits cyclooxygenase 2, which causes a decrease in prostaglandin E2 and nitric oxide (NO) secretion, thus reducing the risk of miscarriage in the first trimester of pregnancy (5).

Recent studies have reported the benefits of oral or intravaginal ALA administration in pregnant women at risk of miscarriage in the first trimester (2,5,42).

A survey reflecting the positive effects of ALA was conducted by Porcaro *et al* (38) on two groups of pregnant women. The study sample consisted of pregnant women in the first 13 weeks of pregnancy diagnosed with threatened or imminent abortion, presenting with subchorionic hematoma occupying between 20% and >50% of the gestational sac surface, vaginal bleeding, lumbar-abdominal pain, or uterine contractions. In the first group, pregnant women received 200 mg vaginal progesterone twice/day, whereas pregnant women in the second group were administered 200 mg vaginal progesterone twice/day combined with 300 mg oral ALA twice/day. The results demonstrated a decrease in symptoms specific to this clinical entity (having a synergistic effect with the vaginal progesterone treatment). A faster improvement in the clinical symptoms was demonstrated in pregnant women who received oral ALA at 600 mg/day combined with progesterone, compared with pregnant women who received vaginal progesterone alone as follows: 89 vs. 71% remission of vaginal bleeding, 78 vs. 43% improvement in pelvic pain after 1 week and 100% remission of symptoms for ALA-treated patients at 3 weeks. Combined ALA/vaginal progesterone treatment was also associated with a faster remission/reduction of the subchorionic hematoma, with a 50% resorption in the first week, and 90% resorption after 15 days (38).

Table I. ALA proven effects on miscarriage/preterm delivery

Study, year	Design	Patient no. and duration	Pregnancy condition	Treatment	Effects	(Refs.)
Parente *et al*, 2014	Randomized double-blind; clinical trial; controlled	300 patients; 14-34 weeks of pregnancy; duration: Until delivery	Preterm uterine contractions	ALA 100 mg/day and magnesium 225 mg/day; 50 patients on placebo	Reduction in the incidence of premature uterine contractions and hospitalization rate	(42)
Porcaro *et al*, 2015	Randomized; clinical trial; preliminary Results	16 patients; 6-13 weeks of pregnancy; duration: Up to the full mending of the clinical picture	Pregnancy with pelvic pain, vaginal bleeding and subchorionic hematomas	ALA orally 600 mg/day + progesterone 400 mg/ day vs. progesterone 400 mg/day (CG)	Decrease in specific symptoms; faster improvement in the clinical picture and in the remission/reduction of the subchorionic hematoma	(38)
Costantino *et al*, 2016	Randomized; clinical trial; controlled	62 patients; 7-12 weeks of pregnancy; duration: 60 days	Imminent abortion in the first trimester	ALA (vaginal capsule) 10 mg/day vs. progesterone (vaginal soft gel) 400 mg/day; CG without treatment (on request)	Faster resorption of subchorionic hematoma; decreased number of miscarriages in the ALA group	(39)
Grandi *et al*, 2017	Randomized; clinical trial; controlled	40 patients; 24-30 weeks of pregnancy; duration: 30 days	Women hospitalized for a first preterm labor episode (cervical change diagnosed by TV US)	ALA (vaginal capsule) 400 mg/day	Vaginal ALA inhibited the cervical effacement after a preterm labor event	(49)
Vitrano *et al*, 2018	Prospective; observational; controlled	60 patients; 24-33 weeks of pregnancy; duration: 30 days orally, 10 days vaginally	Cervical shortening diagnosed by TV US and/or pelvic pain	ALA orally 2x300 mg/day and vaginally 10 mg/day	ALA alleviated the symptoms	(50)

ALA, α-lipoic acid; TV US, transvaginal ultrasound; CG, control group.

Constantino *et al* (39) reported results from a pilot study at the Women's Health Center (Ferrara, Italy). The study group comprised pregnant women with imminent abortion in the first trimester (7-12 weeks of gestation), with or without subchorionic hematoma. The study evaluated the vaginal administration of a preparation containing ALA (10 mg/day). The data were compared with those obtained from pregnant women who received progesterone (400 mg/day) and from the control group (patients who did not receive any medication). The results demonstrated that vaginal administration of ALA resulted in faster resorption of subchorionic hematoma, while avoiding insufficient intestinal absorption (80% resorption of the hematoma in ALA-treated patients at 20 days). Regarding symptomatology (low back pain, pelvic pain and vaginal bleeding), 2 women from the progesterone alone and 3 from the control group still suffered from pelvic pain at the 20-day check-up, whereas ALA-treated patients reported full remission of pelvic pain and vaginal bleeding in the first 20 days of treatment. No significant differences were observed between the study groups receiving treatment. Final assessments were performed on pregnant women who reached 20 weeks of gestation.

Progesterone serves an immunosuppressive role in pregnancy, whereas ALA exerts fine immunomodulatory effects among different cytokines. Therefore, ALA may represent a new therapeutic option in this setting.

Regular uterine contractions between 26 and 37 weeks of gestation are responsible for premature delivery, which represents a public health concern. To date, certain strategies have been developed for early diagnosis and suppression of premature uterine contractions through appropriate treatment. Premature contractions have a multifactorial etiology explained by multiple pathophysiological mechanisms. The treatment regimens must be combined and individualized for each patient. The obstetricians must carefully select the tocolytic agent to ensure maximum efficiency with minimal side effects. The most frequently recommended treatment includes administering calcium antagonists, oxytocin antagonists, prostaglandin synthesis inhibitors, NO donors, betamimetics and magnesium sulfate (43,44).

Although several tocolytic compounds are available, consensus of the optimal first-line tocolytic agent is still lacking. Recent research on innovative, effective and safe therapies describes preparations containing ALA as the missing link (42). This molecule acts as a neutralizer of oxygen free radicals, exhibiting prominent anti-inflammatory and immunomodulatory properties. ALA works synergistically with magnesium in ameliorating/amending premature uterine contractions.

Parente *et al* (42) conducted a study involving 300 pregnant women at 14-34 weeks of gestation, with premature uterine contractions but no vaginal infections, among whom 50 women had a history of miscarriage and premature delivery. The subjects received 100 mg ALA/day and 225 mg magnesium/day. They were followed up on an outpatient basis every 4 weeks, recording events such as sporadic and persistent episodes of premature contractions requiring combined tocolytic therapy and possible hospitalization. The findings demonstrated that the administration of magnesium and ALA starting from the 14th gestational week led to a reduction in the incidence of premature uterine contractions and hospitalization rate. A total of 52% reported the absence of premature uterine contractions throughout the pregnancy, while 28% reported sporadic episodes of uterine contractions that did not require other tocolytic medication.

Experimental studies have shown that the pathophysiological mechanisms involved in the onset and persistence of premature uterine contractions are distinct and they are most commonly associated with the degradation of the extracellular matrix of the cervical membrane (45,46). Myometrial activation may occur with or without the premature rupture of membranes (46). Premature degradation and rupture of amniotic membranes may result from collagen alteration at this level, caused by the TNF-α and thrombin, mediated by certain metalloproteases. Recent *in vitro* studies have shown that ALA inhibits the action of TNF-α and thrombin on the amniotic membrane, thus inhibiting their degradation and fragility (47,48).

The mechanism through which ALA inhibits amniotic membrane degradation remains elusive. It has been shown that ALA inhibits NF-κB, a protein complex that controls the transcription of DNA that is activated by cytokines and thrombin (47).

Therefore, ALA has antioxidant and NF-κB-inhibitory properties, and its association with magnesium counteracts premature uterine contractions and prevents premature rupture of amniotic membranes, lowering the hospitalization rate in these women. However, the precise effects of this combination must be verified in a significantly larger number of subjects.

ALA may protect against premature cervical shortening. Thus far, when addressing preterm birth, we can only intervene on uterine contractility with tocolytic drugs; however, not all the pathophysiological elements can be assessed and resolved. The imbalance between pro-inflammatory and anti-inflammatory cytokines may serve as a foundation for premature cervical shortening. Recent studies analyzed the inflammatory mediators synthesized by fetal tissues and the maternal genital tract and their preterm delivery role (49,50). Compiled information suggests that infection and inflammation are latent causes determining preterm birth (51). The subtle and defining changes observed in these women are associated with modifications/alterations in the cervicovaginal fluid composition and qualities. Increased local levels of pro-inflammatory cytokines, such as IL-8, prostaglandins and MMPs (mainly MMP-9) are involved in the process of cervical ripening by inducing changes in the extracellular matrix (50).

The efficiency of ALA in reducing the expression of MMP-9 and inhibiting the TNF-α- and thrombin-induced reduction in the strength of human fetal membranes has been previously reported (47,48,52).

Grandi *et al* (49) conducted a pilot study and concluded that ALA administered vaginally maintained the length of the cervix and kept it closed after an episode of preterm labor. The survey included 40 pregnant women at 24-30 weeks of pregnancy, 20 of whom received 400 mg ALA administered vaginally for 30 days. The main finding of the study was that vaginal ALA administration exerted a distinct anti-inflammatory effect at the cervical level compared with placebo. In the treatment group, the monthly cervical shortening was arrested

at the normal expected values of 3 mm, whereas double this rate was observed in women receiving placebo (48). ALA treatment is strongly associated with the stabilization of the cervix, which typically undergoes shortening. As regards tolerability, transient vaginal discomfort was reported by 2 patients from the vaginal ALA group.

In a prospective observational study, Vitrano *et al* (50) tested the effects of ALA on women at risk of preterm birth, with cervical shortening diagnosed by transvaginal ultrasound and/or pelvic pain. The survey included 60 pregnant women at 24-33 weeks pregnancy in two groups: 50 patients received combined oral ALA at 2x300 mg/day for 30 days and vaginal ALA at 10 mg/day for 10 days, and 10 patients refused the treatment. A total of 44 patients had symptoms, 40 of whom received ALA and 37 reported amelioration, while 3 patients did not display any improvement. In the 4 untreated patients, the clinical symptoms persisted. These results support ALA supplementation for reducing the risk of preterm labor onset and symptomatology and for delaying cervical shortening in women at risk of preterm delivery. ALA administered at therapeutic doses was safe and was not associated with major side effects.

As the surveys conducted to date included small sample populations, the success of ALA in preventing threatened preterm delivery requires further validation in extended groups of patients to ratify therapy effectiveness.

Future prospects. Pregnancy represents a metabolic challenge characterized by increased metabolic rate and increased mitochondrial activity, with the placenta itself being a source of oxidative stress. Stress is triggered by the imbalance between free radicals (oxidants) and antioxidants (52,53), testing the ability of the body to eliminate the amount of reactive oxygen species. The ability of placental antioxidants to attenuate potentially harmful free radicals is crucial for normal placental function and optimal fetal growth and development (54).

Preeclampsia is a dysfunction caused by abnormal placentation and an excessive maternal inflammatory vascular response. The mechanisms that determine the evolution towards preeclampsia are numerous, some of which remain incompletely understood.

Abnormal cytotrophoblast invasion in spiral arterioles leads to inappropriate vascular remodeling, endothelial cell dysfunction and placental insufficiency. Preeclampsia leads to extreme hypoxia in the placental bed and an exaggerated oxidative reaction with the release of oxygen free radicals (55,56), the source of which are the placental mitochondria (57). Exaggerated lipid peroxidation reactions occur, along with increased xanthine oxidase levels in the blood, placental tissue and umbilical cord. At the placental endoplasmic reticulum level, faulty protein synthesis occurs, which leads to cell apoptosis. This pathway is considered to contribute to intrauterine growth restriction and the development of cytokine and prostaglandin-induced preeclampsia (58).

The association between fetoplacental hypoxia, oxidative stress and fetal brain impairment during the perinatal period represents information validated by extensive research with specific topics (59,60). When there is a variation in the placental blood flow or placental insufficiency, a series of mechanisms help the fetus cope with the acute or chronic reduction in oxygen availability. Tissue hypoxia caused by hypoxemia, hypoperfusion, and ischemia/reperfusion generates an excess of oxygen free radicals and causes a decrease in the antioxidant defense capacity. Under these conditions of increased oxidative stress, the fetal tissues, particularly the fetal brain, are exposed to the deleterious effects of free radicals (60).

Traditionally, it has been accepted that this imbalance leads to cell damage by the accumulation of reactive oxygen species in tissues, oxidation of lipids and intracellular proteins, resulting in cell death by apoptosis or necrosis (59-61). Overproduction of free radicals triggers a systemic inflammatory response in the fetal body, given the already compromised oxygen availability.

As oxidative stress plays a key role in developing preeclampsia and intrauterine growth restriction, antioxidant supplementation may prove essential for disease prevention.

Taking into consideration all these aspects, the administration of an antioxidant with a fetal neuroprotective role may represent an innovative therapeutic strategy. Recent theories have reinforced the concept that antioxidants, such as ALA, can protect the fetus against oxidative stress, particularly towards the end of pregnancy. ALA has a low molecular weight and an increased ability to cross biological membranes, including the blood-brain barrier. Its efficiency depends on the dose, administration route, and the time elapsed between treatment administration and the onset of hypoxic cerebral injury. A study in rats and mice conducted by Wolz and Krieglstein (62) reported that ALA acted as a neuroprotector when administered subcutaneously, and was most effective when administered 2 h prior to occlusion of the middle cerebral artery. In 2017, Mei and Yang (63) demonstrated the antioxidant and anti-inflammatory role of ALA in mice with cerebral hypoxia and evolution to hypoxic-ischemic encephalopathy. Administering ALA 7 days prior to injury was associated with a decrease in the volume of the cerebral infarct, the degree of cerebral edema, and the levels of several inflammatory markers involved in oxidative stress, such as TNF-α, NF-p65, IL-1β and IL-6. In addition, a secondary increase in the expression of certain antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) was also observed.

4. Conclusions

ALA/DHLA acts as potent immunomodulatory redox couple, with a specific role in preventing miscarriage and premature delivery. The administration of ALA may represent a promising therapeutic strategy in several obstetric pathologies, such as complicated pregnancies with abnormal placentation/exaggerated maternal vascular inflammatory response (15), or hypoxia/perinatal ischemia caused by various factors (64). Validation of this therapeutic indication requires further studies. The onset of hypoxic or ischemic injury should be diagnosed accurately to determine the appropriate timing and dose for ALA administration.

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Authors' contributions

AP, MB and MEZ designed the review. NM, IGC, AB, MCD, RCP and FS performed the literature research and drafted the manuscript. AP, MB, NM and MEZ substantially contributed to the conception of the study, revised and edited the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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