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Comparison of Vaginal Progesterone Alone with Vaginal Progesterone in Combination with Alpha Lipoic Acid for Prevention of Preterm Birth

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ABSTRACT

Background: The etiology of preterm labor is complicated. Fetal membrane activation, cervical abnormalities, abdominal pain, and spontaneous uterine contractions are all associated with an inflammatory response. Premature birth is closely connected with cervical shortening throughout the second quarter of pregnancy. We assessed the advantages of administering alpha lipoic acid to women who were deemed to be at risk of preterm delivery due to a history of preterm birth. **Methods**: Patients presenting at the Gynecology and Obstetrics Department, Allied Hospital, Faisalabad from Sep 2024 to 28 Feb 2025 were included in this prospective study. Group A patients were given vaginal suppository of micronized progesterone alone (Cyclogest 400 mg vaginal pessary) nightly before bedtime until delivery. Group B patients were given vaginal progesterone in combination with oral alpha lipoic acid; Cyclogest 400 mg vaginal pessary with 2 tablets Alapro (containing 300 mg alpha lipoic acid) daily until delivery. Efficacy of the treatment was assessed by the absence /presence of preterm births. **Results**: Among 140 pregnant females, 70 belonged to each group. In Group A, 66 patients delivered after 37 weeks while in Group B, 56 patients delivered after 37 weeks. (p-value <0.05). **Conclusion**: In our group of patients, oral alpha lipoic acid supplementation with vaginal progesterone was more efficacious than vaginal progesterone alone at preventing premature birth. During the course of treatment, no negative effects were found.

INTRODUCTION

Preterm labor, an ongoing health concern, impacts 5-17% of all pregnancies. Prematurity is one of the primary causes of neonatal morbidity and mortality. Preterm labor is defined as the onset of regular uterine contractions with progressive effacement and dilatation of the cervix before to 37 complete weeks of pregnancy. Preterm labor is a complicated syndrome caused by a number of etiologic processes, including infection/inflammation, vascular disorders, decidual hemorrhage, uterine overdistension, decreased progesterone action, cervical disease, breakdown of maternal fetal intolerance, immunologically mediated processes, and maternal stress, among others. Preterm birth rates are higher in poorer countries than in industrialized ones, making prevention an important public health priority. Women who have had spontaneous preterm birth (sPTB) experience a recurrence in 21-57% of their subsequent pregnancies and are considered a high-risk population.[1]

A complex Interplay between the host's immune system and the microbial environment may be the cause of preterm delivery rather than just infection. The fetal tissues and the mother's vaginal canal manufacture and secrete a variety of inflammatory mediators, including pro-inflammatory cytokines, prostaglandins, and mostly MMP-9. Furthermore, a high association with the inflammatory response was observed in almost 40% of patients.[2]

According to earlier studies, vaginal progesterone is effective for asymptomatic pregnant women with a short cervix.[3] It is critical to discover a medicine that can significantly postpone premature birth in this circumstance while causing negligible or no adverse effects, even when symptoms (uterine hypercontractility) exist. At therapeutic doses, alpha lipoic acid, an organosulfur compound with the molecular weight 206.32, is a naturally safe molecule with a variety of pleiotropic qualities. Reed et al. isolated it after chemical extraction.[4] Plants and animals produce alpha lipoic acid, but humans produce very little; the richest tissues have high mitochondrial concentration.[5] Numerous immunomodulatory characteristics of alpha lipoic acid have been shown to help avoid preterm birth.[6] Our study aimed to assess the effects of alpha lipoic acid supplementation in pregnant women who were at risk of

preterm birth.

MATERIALS AND METHODS

This is a cross-sectional prospective study conducted from to after approved from the Institutional Ethical Committee. The research comprised 140 patients (70 in each group) from the Department of Gynecology and Obstetrics at Allied Hospital, Faisalabad who had previous history of preterm birth and met the inclusion criteria. Each patient provided a detailed history as well as signed informed permission.

All the patients were randomly divided into two groups by using computer generated random number table. Group A patients were given vaginal suppository of micronized progesterone alone (Cyclogest, 400 mg pessary) nightly before bedtime until delivery. Group B patients were given vaginal progesterone in combination with oral alpha lipoic acid; Cyclogest 400 mg vaginal pessary with 2 tablets Alapro (containing 300 mg alpha lipoic acid) daily until delivery. Patients were followed by taking their contact number until their delivery. Efficacy of the treatment was assessed by the number of term births.

Inclusion Criteria

- Pregnant females aged between 18-40 years
- Patients with ≥24 weeks of gestation
- Previous history of preterm birth
- Absence of bacterial vaginosis.

Exclusion Criteria

- Patients having premature rupture of membranes
- Pre-existing diabetes mellitus or systolic pressure ≥140 mmHg at the enrolment
- Diagnosis of diseases such as cancer, lupus, hepatitis, HIV/AIDS
- Multiple pregnancies
- Preeclampsia and cardiovascular disease
- Short cervix <25 mm
- Contraindications/allergy to study drugs

Data Analysis

Sample size was calculated by using WHO sample size calculator of two proportions with P1 = 98.5% and P2= 87.5% taking level of significance =5%, confidence level =95% and power of the test =80%, the sample size was determined to be 140 (70 patients were in each group). Data was analyzed using a statistical analysis tool (IBM-SPSS V-23). For quantitative variables such as age, BMI, gestational age and parity, Mean +/-SD was calculated. Frequency was computed for qualitative variable such as number of preterm births determining efficacy of the treatment. Chi square test was applied to compare efficacy between the two groups with p-value <0.05 being considered statistically significant.

RESULTS

The mean ±SD age of patients was 29.028±2.82 years in Group A (patients who took vaginal progesterone and oral alpha lipoic acid) and 28.885±2.89 years in Group B (patients who took vaginal progesterone alone) with p-value 0.768. The mean ±SD of gestational age in Group A was 34.414±1.16 weeks while in Group B was 34.457±1.17 weeks (p-value 0.829). The mean ±SD of parity of pregnant females in Group A was 2.70±0.74 and Group B was 2.94±0.81 (p-value 0.068). The mean ±SD of BMI in Group A was 28.985±2.80 kg/m^2 and Group B was 29.028±2.81 kg/m^2 (p-value 0.928). See Table 1. In Group A, 94.28% of pregnant females delivered at term (after 37 weeks) while 80% of pregnant females delivered at term in Group B. Efficacy of the treatment with oral alpha lipoic acid along with vaginal progesterone on the number of term births was statistically significant with lesser frequency of preterm births (babies born before 37 weeks of gestation) when compared to vaginal progesterone given alone to pregnant females (p-value <0.05). See Table 2. No complications or side effects were noticed after giving oral alpha lipoic acid.

Table 2

Demographics of Patients in Both Groups (n=140)

Demographics	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
Age (years)	29.028 ± 2.82	28.885 ± 2.89	0.768
Gestational age (weeks)	34.414 ± 1.16	34.457 ± 1.17	0.829
Parity	2.700 ± 0.74	2.942 ± 0.81	0.068
BMI (Kg/m²)	28.985 ± 2.80	29.028 ± 2.81	0.928

Figure 1

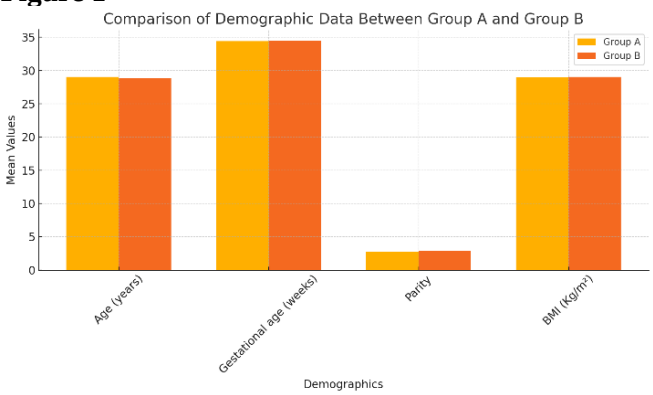
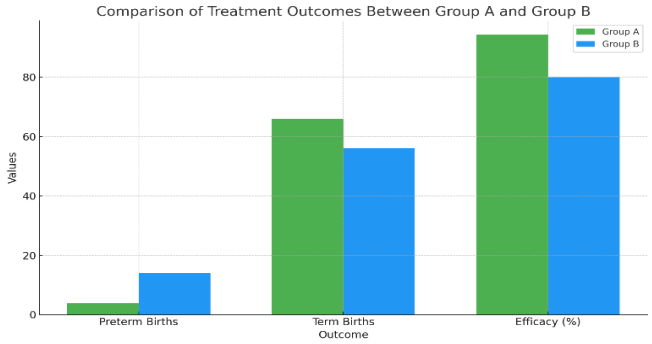


Table 2

Comparison of Efficacy of the Treatment in Both Groups of Patients (n=140)

Outcome	Group A (n = 70) (Vaginal progesterone + oral ALA)	Group B (n = 70) (Vaginal progesterone alone)	p-value
Number of Preterm Births	4	14	0.012
Number of Term Births	66	56	—
Efficacy of Treatment (%)	94.28%	80%	—

Figure 2



DISCUSSION

The results of our study show that in women with a history of preterm birth, alpha lipoic acid supplementation in conjunction with vaginal progesterone throughout the third trimester was helpful in avoiding premature birth. Alpha lipoic acid treatment was safe at therapeutic levels in pregnant women with no negative effects, which is consistent with earlier research.[7,8] The measure of an effective treatment was the birth that occurred after the last monitoring (34 weeks of gestation). According to the updated classification standards, it is "late preterm" and is associated with a much better prognosis and survival rate than births that took place in the preceding weeks. Pro-inflammatory cytokines, prostaglandins, and matrix metalloproteinase (mostly MMP-9) are among the inflammatory mediators that are produced and secreted in the fetal tissues and maternal vaginal canal during premature delivery.[9,10,11,12]

As a pro-inflammatory cytokine, IL-8 appears to be the most involved in the process of cervical ripening, along with matrix metalloproteinase-9, which stimulates extracellular matrix disintegration, and prostaglandin E2.[13] The effect we discovered is supported by previous research on alpha lipoic acid action. Some investigations found that alpha lipoic acid can reduce the expression of matrix metalloproteinase (MMP-9) and counteract TNF-induced and thrombin-induced weakening of human fetal membranes.[14] In vitro, alpha lipoic acid treatment reduced the release of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 caused by LPS stimulation in rat mesangial cells.[15] Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) inhibition resulted in a comparable drop in prostaglandin E2 (PGE2) and nitric oxide (NO) levels as a result of alpha lipoic acid pre-treatment. Furthermore, alpha lipoic acid reduces the expression of the inflammatory cytokine IL-8 while increasing IL-10 mRNA.[16,17] Furthermore, recent clinical trials have confirmed alpha lipoic acid's efficacy as an immunomodulatory molecule for treating some inflammatory conditions during pregnancy. Porcaro et al. conducted a randomized controlled clinical trial in pregnant women at risk of miscarriage.[18] The trial group received alpha lipoic acid (600 mg/day) orally along with progesterone-containing vaginal suppositories, whereas controls received simply progesterone vaginally. The goal was to see if progesterone medication may promote the healing of subchorionic hematomas while also reducing subjective and objective symptoms such vaginal bleeding, abdominal pain, and uterine contractions. The trial demonstrated that alpha lipoic acid plus progesterone significantly improved hematoma resorption compared to progesterone alone.[18] Compared to controls, the study group saw a quicker decrease or elimination of all symptoms; nevertheless, this difference was not statistically significant.

Costantino et al. conducted a controlled randomized clinical trial in women with impending miscarriage to assess the efficacy of alpha lipoic acid (10 mg/day) or progesterone (control) delivered vaginally on subchorionic hematoma resorption.[19] In the alpha lipoic acid-treated group, the subchorionic hematoma was considerably reabsorbed faster than in progesterone patients. It is worth noting that the alpha lipoic acid group experienced fewer miscarriages than the control group as proved by a study done by Grandi et al.[20] All of these impacts support our findings and provide a compelling explanation. Our results support the literature's conclusions that obesity is substantially associated with a lower response to therapy and, as a result, a higher risk of preterm delivery when it comes to high BMI.

CONCLUSION

This study found that the combined use of oral alpha lipoic acid and vaginal progesterone was more effective than vaginal progesterone alone in preventing preterm deliveries in patients at risk of preterm birth. This new treatment's success in threatened preterm delivery is positively associated with a history of previous preterm birth and a high mother BMI. Our study has some clear limitations. The small sample size weakens the study's power, undermining its encouraging findings. The low occurrence of this pathology, and hence the low incidence of positive obstetric history of preterm birth, necessitates the implementation of a multicenter trial to obtain a sufficient sample size.

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