Oral plus vaginal alpha-lipoic acid in women at risk for preterm delivery

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ABSTRACT *— OBJECTIVE: The etiology of preterm labor is multifactorial. An inflammatory response is always involved with the activation of NF-kB that determines synthesis and release of inflammatory molecules, implicated in fetal membrane activation, cervical modifications, abdominal pain and spontaneous uterine contractions. There is a close relationship between preterm birth and cervical shortening in the second quarter of pregnancy. We evaluated the benefits of alpha-lipoic acid administration on women considered at risk of preterm delivery due to the presence of symptoms (pelvic pain and uterine contractions) or reduced cervical length.*

PATIENTS AND METHODS: This prospective observational study was carried out at the Gynecology and Obstetrics Unit of Palermo University Hospital (Palermo, Italy), from October 2015 to April 2016. The inclusion criteria were: women aged 18-35, with gestational age between 24 and 33 weeks of amenorrhea, pregnancy at risk of preterm delivery due to cervical length between 35-25 mm (in presence of symptoms) or < 30 and > 15 mm (if asymptomatic), intact membranes and negative for vaginosis. Patients were treated daily with alpha lipoic acid orally (300 mg, twice a day for 30 days) and vaginally (10 mg, once a day for 10 days), or untreated (controls). Patients were evaluated at the baseline (T 0), after 7 days, after 30 days, and at 34 weeks of gestation considering: maternal characteristics, symptomology and cervical length.

RESULTS: Among 60 analyzed women, 50 were treated orally and vaginally with alpha-lipoic acid, whereas 10 did not undergo any therapy. In the treated group, 10 patients were asymptomatic and 40 symptomatic. The symptoms disappeared in 37 patients. In the untreated group, 4 women were symptomatic and 6 asymptomatic. At the end all women were symptomatic. Mean cervical length showed a reduction in the untreated group compared to the treated group.

CONCLUSIONS: The vaginal/oral-combined administration with alpha-lipoic acid showed effectiveness in reducing symptoms and preventing cervical shortening in our set of patients. No adverse effects were detected during the treatment.

KEYWORDS
Preterm labor, Cervicometry length, Transvaginal ultrasound, NF-kB, Interleukin-1, Matrix metalloproteinases, Prostaglandin E2.

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INTRODUCTION

Preterm delivery is characterized by the onset of regular uterine contractions in association with progressive cervical shortening and dilatation. Premature activation of fetal membranes (FM) and remodeling of cervical collagen are the main events that speed up preterm birth[1]. According to WHO, preterm is defined as babies born alive before 37 weeks of pregnancy are completed.

In most of the developed countries its incidence goes from 5% to 10%. Preterm birth may be associated with neonatal complications, which can appear forthwith or later. Disorders such as neurodevelopmental delay, cerebral palsy and chronic lung disease are the major consequences for long-term morbidity. The neonatal outcome is linked to the gestational age at childbirth and associated features (i.e. infections). Obviously, the risk of mortality and morbidity grows in inverse proportion to the increase of gestational age. The prevention and treatment of preterm labor need that the expectant mothers at risk are identified on time; this diagnosis remains a key challenge. The risk of preterm delivery increases with the length reduction of uterine cervix. For this reason, the measurement of cervical length can be used as a predictor. The transvaginal ultrasound (TVS) is the most reliable technique for measuring the cervical canal. It is the first-choice method for evaluating the cervical length finalized to identify women with singleton pregnancy at risk of preterm delivery.

The etiology of this complication is multifactorial; however, the mechanism underlying such process has still to be wholly understood. The infection alone may be insufficient to cause preterm birth, which is often the result of a complex interaction between microbial environment and immune response activated by the host. In this way, many inflammatory mediators are synthesized and secreted in the maternal genital tract and fetal tissues; among such mediators pro-inflammatory cytokines, prostaglandins and matrix metalloproteinase (mainly MMP-9) play a crucial role[2]. Furthermore, a close relationship with the inflammatory response was demonstrated in over 40% of cases. In this context also, the oxytocin receptors were found to play an inducing role. Current treatments take advantage of corticosteroids and tocolytics (beta-mimetics, calcium channel blockers, non-steroidal anti-inflammatory drugs). However, antenatal corticosteroid administration was proven detrimental in various respects[3-5]. On the other hand, since preterm birth is caused by several factors, such as early activation of cervical ripening, and decidua, as well as uterine contractility, tocolytic drugs are not able to intervene on all the pathophysiological elements. Namely, tocolytic agents act only by reducing more or less drastically, contractile uterine activity and, therefore, they can't alone decrease the incidence of premature delivery[6]. Previous evidence demonstrated the efficacy of vaginal progesterone in asymptomatic women affected by short cervix at mid pregnancy[7]. In this context it is important to identify a therapy, which is able to delay in substantial manner, preterm delivery with very reduced or absent adverse effects, even in presence of symptoms (uterine hypercontractility).

Alpha-lipoic acid (ALA) is an organosulfur compound with MW 206.32, a natural safe molecule at therapeutic doses, having several pleiotropic actions. It was isolated and chemically identified by Reed et al[8]. ALA is synthesized in plants and animals, but its production in humans is very low; tissues characterized by the presence of numerous mitochondria are the richest[9]. Potatoes, broccoli, spinach, tomatoes, Brussels sprouts, peas, and brown rice contain great quantities of this compound, but red meat (especially liver, heart, and kidney) is the most relevant source[10]. ALA was shown to exert a number of immunomodulatory activities useful for preventing preterm delivery[11].

Based on these premises, our study was aimed at testing ALA administration in women at risk of preterm birth.

PATIENTS AND METHODS

This prospective observational study was carried out at the Gynecology and Obstetrics Unit of Palermo University Hospital (Palermo, Italy), from October 2015 to April 2016. It was approved by the Ethics Committee of our hospital.

Primary outcome of this trial was to evaluate the efficacy of ALA in decreasing the symptomatology affecting the patients and counteracting the process of cervical shortening. Patients were recruited from the 24th to 33rd week based on the cervicometric evaluation with transvaginal ultrasound, and/or the presence of pelvic pain.

Pregnant women who turned to our clinic, were included among treated or untreated subjects without randomization, obtaining a respective final ratio of 5:1. The control group was made up with patients who refused to be administered with ALA.

Women were asked to complete questionnaires focused on general health, behaviour and lifestyle, diet and drug use (spasmolytic/tocolytics) in previous pregnancies.

Inclusion criteria:

- aged between 18-35 years;
- 24-33 weeks gestation;
- intact membranes;
- cervical length between 35-25 mm (in presence of symptoms) or < 30 and > 15 mm (if asymptomatic);
- absence of bacterial vaginosis.

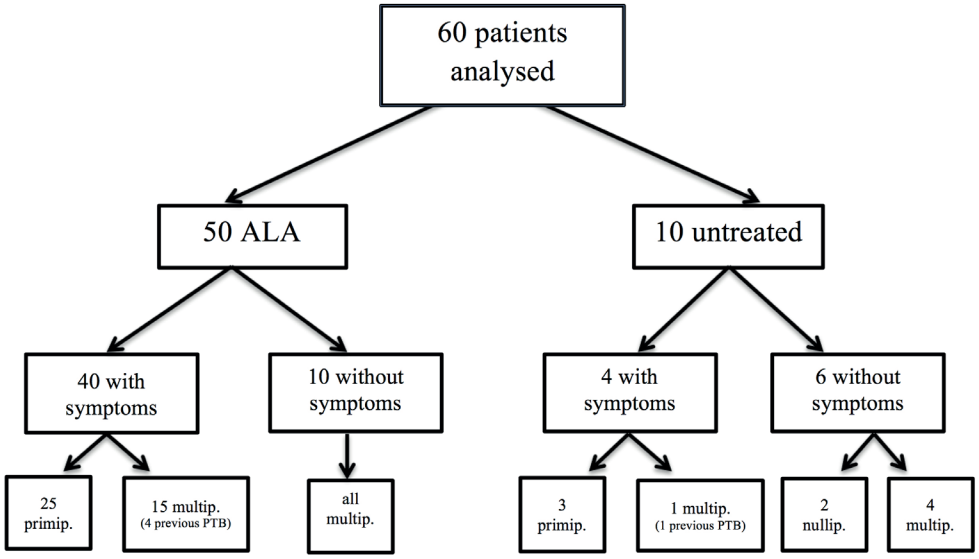


Figure 1. Flow chart of the study and patients' characteristics

Exclusion criteria:

- pregnancy at high risk;
- pre-existing diabetes mellitus or systolic pressure ≥140 mmHg at the enrolment;
- diagnosis of diseases such as cancer, lupus, hepatitis, HIV/AIDS;
- alcohol abuse, drug use;
- positive swab for bacterial vaginosis, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*;
- previous treatments with tocolytic agents or progestogens in the last 8 weeks.

All patients were made aware about the treatment and risks. Moreover, they were informed to be not eligible for a different therapy. All patients signed an informed consent.

Maternal characteristics (obstetric history, age, BMI, smoking, race) were recorded at the enrolment day (T0). The treatment consisted of one vaginal capsule/die (DAV® vaginal capsules, Lo.Li. Pharma srl (Rome, Italy), containing 10 mg ALA each capsule) per 10 days and two oral tablets/die (DAV®, Lo. Li.Pharma srl, Rome, Italy, containing 300 mg ALA each tablet) per 30 days.

The included patients were further subdivided according to the presence of symptoms of prematurity into two sub-groups: symptomatic or asymptomatic. These two groups were followed up until delivery. The clinical and instrumental monitoring was carried out at the following times:

T0: enrolment day; T1: after 7 days; T2: after 30 days; T3: at 34 weeks of gestation.

Each control comprised cervicometric evaluation with transvaginal ultrasound, cardiotocographic trace to monitor uterine contractions, assessment of possible vaginal bleeding and/or membrane rupture. The comparison between the two groups was performed by means of the Fisher's exact test. The p-value <0.05 was considered statistically significant. Then, a logistic regression model was developed for all study variables.

RESULTS

This clinical study enrolled 60 healthy pregnant women aged between 21 and 33 years. They were included into two groups: 50 patients received the combined oral and vaginal ALA-based treatment and 10 were untreated (Fig. 1). At the recruitment, in the treated group, 10 patients were asymptomatic and 40 symptomatic (pelvic pain). The 10 asymptomatic patients were all multiparas with previous full-term pregnancy: all these patients remained asymptomatic throughout pregnancy. Among 40 symptomatic women, 25 were primiparas and 15 multiparas.

During the observational period, only one primiparous remained symptomatic, but she still gave birth after 34 weeks, therefore after the last follow up. Among the 15 multiparas, 4 of them had had a previous preterm birth (before 34 weeks). In this last group of patients (multiparous, symptomatic and with a history of PTB) two remained symptomatic, one giving birth before 34 weeks, and the other one at term.

Therefore, among the 40 symptomatic women, 37 got benefit by the therapy and become asymptomatic, whilst 3 of them remained symptomatic but only one gave birth before 34 weeks.

Overall in the treated group only one patient delivered before 34 weeks. She was multiparous with a history of previous PTB.

In control group, 6 patients were asymptomatic and 4 were symptomatic; among the latter, 3 were primiparas and among them, 2 remained symptomatic and gave birth after 34 weeks, whereas 1 contin-

Table 1. Symptoms and pregnancy outcome according to groups.

Patients' characteristics				Outcomes		
Patients (n)	Treatments	Symptoms at T0	Parity and history of PTB	Symptoms	Delivery	
					≤ 34 weeks	> 34 weeks
60	50 ALA	40 with symptoms	25 primiparas	1 patient: symptoms lasted during the study		1
				24 patients: symptoms disappeared during the study		24
			15 multiparas (4 previous PTB)	2 patients: symptoms lasted during the study	1 (previous PTB)	1
				13 patients: symptoms disappeared during the treatment		13
		10 without symptoms	10 multiparas	10 patients: no symptoms occurred throughout the study		10
	10 untreated	4 with symptoms	3 primiparas	3 patients: symptoms lasted during the study	1	2
			1 multiparous (1 previous PTB)	1 patient: symptoms lasted during the trial	1	
		6 without symptoms	2 nulliparas	2 patients: symptoms appeared during the study		2
			4 multiparas	4 patients: symptoms appeared during the study		4

ued to be affected by symptoms and delivered at 32 weeks. Among the symptomatic women, only 1 was multiparous with previous PTB before 28 weeks; she remained symptomatic, and gave birth at 28 weeks. Therefore, between 4 symptomatic untreated patients, they all continued to be affected by symptoms and 2 of them delivered before 34 weeks. In the 6 asymptomatic untreated women (2 nulliparous and 4 multiparas), symptoms appeared during the study; however, birth occurred after 34 weeks (Table 1).

Treatment efficacy was evaluated and resulted significant both in maintaining the absence of symptoms and in decreasing them (Table 2a and b).

Between the two groups (treated and untreated) asymptomatic patients were 16; 10 of them were treated and all remained stationary, instead 6 were not treated and all of them showed a worsening of symptoms. Between the two groups (treated and untreated), symptomatic patients were 44; 40 received ALA and 37 of them reported a symptoms improvement, only three did not show any variation. In the remaining 4 subjects (without treatment) the situation remained unchanged. Mean cervical length showed a significant lessening between T0 and T3 in the untreated group compared to the treated one. Among ALA patients, at recruitment mean cervical length was 29.82 mm; at T3 it was 28.93 mm (reduction: 2.98%). Instead, in the untreated group it was 29.7 mm and then 26.25 mm (reduction: 11.6%).

Table 2a. Symptoms evaluation in asymptomatic patients.

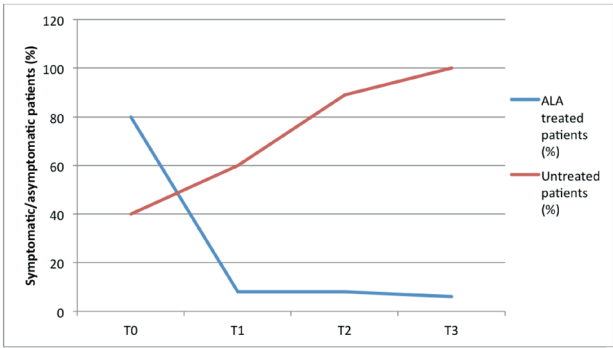
Asymptomatic patients at T0	Stationary	Worsened	Total
Treatment	10*	0	10
No treatment	0	6	6
	10	6	16

*Fisher's exact test: p-value = 0.001 *vs*. no treatment.

Table 2b. Symptoms evaluation in symptomatic patients.

Symptomatic patients at T0	Improved	Not improved	Total
Treatment	37*	3	40
No treatment	0	4	4
	37	7	44

*Fisher's exact test: p-value = 0.001 *vs*. no treatment.



Monitoring time	% of symptomatic patients in ALA group	% of symptomatic patients in untreated
T0	80	40
T1	8	60
T2	8	89
T3	6	100

Figure 2. Comparison of symptoms overtime per group.

Comparison of symptoms over time

In the graph can be seen the symptoms improvement of the treated patients, at T0 (enrolment day), T1 (after 7 days), T2 (after 30 days) and T3 (at 34 weeks of gestation) (Fig. 2). At the recruitment (T0) 80% of women to be administered with ALA, was symptomatic, whereas at T3 only 6% were still symptomatic and 94% remained or became asymptomatic. Instead, at the recruitment (T0) 40% were symptomatic in the control group and at T3 100% became symptomatic. We subsequently developed a logistic regression model to figure out if the symptoms improvement was induced only by the treatment or was influenced by other variables too (Table 3). The *p*-value showed that there were no significant differences by race and maternal age and that at T1 the symptoms were almost exclusively influenced by the treatment, while at T3 other variables such as BMI ($p<0.013$), smoking ($p<0.025$) and obstetric history ($p<0.014$) became significant in conditioning the response to the treatment.

Comparison of cervical length over time

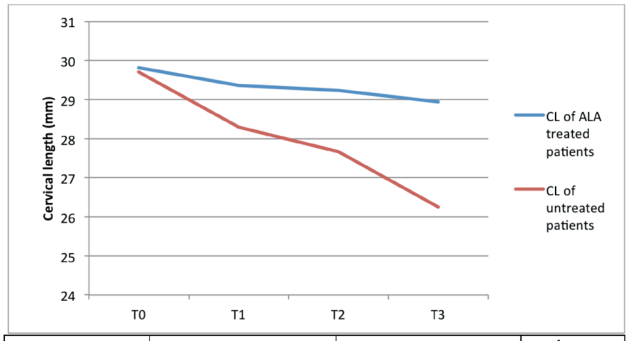
The averages of the cervical length were calculated and compared between the groups, at T0 (enrolment day), T1 (after 7 days), T2 (after 30 days) and T3 (at 34 weeks of gestation) (Fig. 3). The graph shows that over time the treated patients had a minor reduction of the cervical length compared to the untreated ones. At the recruitment, in the ALA group the mean cervical length was 29.82 mm; at T3 28.94 mm (percentage reduction: 2.98%), instead in the untreated group the mean cervical length was 29.7 mm at T0 and 26,25 mm at T3 (percentage reduction: 11.6%). The difference between the two groups at T3 was found significant (*p*-value = 0.006).

Finally, the logistic regression model was used again to figure out if the smaller lessening of the cervical canal in the treated group was only due to the treatment or was caused by other variables.

The *p*-values show that at T3 the different decrease of the cervical length is determined not only by the treatment, but also by other factors, such as BMI ($p<0.000$), smoking ($p<0.024$), previous preterm birth ($p=.000$).

Table 3. Logistic regression model related to symptom (pelvic pain) at T1 and T3

Pelvic pain T1	Coef.	Std.Err.	t	P>|t|	95% Conf.	Interval
Age	.0108625	.0177976	0.61	0.544	-.0248851	.0466101
BMI	.0252463	.014709	1.72	0.092	-.0042976	.0547903
Race	-.0339228	.0454798	-0.75	0.459	-.1252718	.0574261
Smoking	.1349882	.0994971	1.36	0.181	-.0648576	.3348339
Primiparous	-.0763835	.1557947	-0.49	0.626	-.3893064	.2365394
Previous Preterm Birth < 34 weeks	.4394954	.2368892	1.86	0.069	-.0363105	.9153013
Previous Preterm Birth > 34 weeks	-.0565818	.2160546	-0.26	0.794	-.4905402	.3773766
Previous Term Birth	-.0939638	.1613254	-0.58	0.563	-.4179955	.2300678
Treated	-.4314717	.0954872	-4.52	0.000	-.6232634	-.23968
_cons	-.3588863	.6223751	-0.58	0.567	-1.608963	.8911908
Pelvic pain T3	**Coef.**	**Std.Err.**	**t**	**P>|t|**	**95% Conf.**	**Interval**
Age	.0175693	.0113661	1.55	0.128	-.0052602	.0403987
BMI	.0242824	.0093936	2.58	0.013	.0054147	.04315
Race	-.0254152	.0290448	-0.88	0.386	-.0837534	.0329229
Smoking	.1472408	.0635417	2.32	0.025	.0196135	.2748681
Primiparous	.1439646	.0994951	1.45	0.154	-.0558772	.3438063
Previous Preterm Birth < 34 weeks	.3841629	.1512844	2.54	0.014	.0802993	.6880265
Previous Preterm Birth > 34 weeks	.366513	.1379788	2.66	0.011	.0893744	.6436515
Previous Term Birth	.1880698	.1030271	1.83	0.074	-.0188664	.3950059
Treated	-.8447964	.0609809	-13.85	0.000	-.9672802	-.7223126
_cons	-.3684833	.397467	-0.93	0.358	-1.166819	.4298526



Monitoring time	CL of ALA patients mean ± SD	CL of untreated patients mean ± SD	*p*-value
T0	29.82 ± 2.6	29.70 ± 2.0	0.5
T1	29.36 ± 2.6	28.30 ± 1.7	0.8
T2	29.24 ± 2.5	27.67 ± 1.0	0.5
T3	28.94 ± 2.5	26.25 ± 1.2	0.006

Figure 3. Comparison of mean cervical length (CL) overtime per group.

DISCUSSION

This study showed that ALA supplementation during the second trimester has proven effective in reducing the symptomatology as well as in preventing both the onset of symptoms and the cervical shortening in women at risk of preterm delivery. In agreement with previously reported studies[11,12], ALA administration was safe at therapeutic doses in pregnant women, without any adverse effect.

Birth after the last monitoring (34 weeks of gestation) was considered as parameter of efficacious treatment. The new classification criteria consider it "late preterm" as correlated with significantly higher prognosis and survival rate than the childbirths occurring in the previous weeks. One of the most important parameters for medical history evaluation of the examined patients was a positive obstetric anamnesis for previous preterm birth. In fact, treatment with ALA was successful in reducing preterm delivery rate before 34 weeks in women with negative obstetric anamnesis and in those with previous moderate preterm birth, whereas it showed a relative efficacy in women with previous "low preterm" delivery. This may be related to the multifactorial aetiology of preterm labor. Despite the knowledge of its etiopathogenesis is considerably improved in the last decades, many of the underlying mechanisms remain to be elucidated. As mentioned before, in preterm delivery inflammatory mediators are synthesized and secreted in the maternal genital tract and fetal tissues; among such mediators pro-inflammatory cytokines, prostaglandins and matrix metalloproteinase (mainly MMP-9) play a crucial role[2]. As pro-inflammatory cytokine, IL-8 looks to be the most involved in the process of cervical ripening[13], as well as matrix metalloproteinase-9[14], which induces the degradation of the extracellular matrix, and prostaglandin E2[15]. Previous data concerning ALA activity support the effect we found. Some researches and studies demonstrated ALA efficacy in reducing the expression of matrix metalloproteinase (MMP)-9[16] and in countering TNF-induced and thrombin-induced weakening of human foetal membranes[17,18]. Moreover, ALA administration *in vitro* lessened the secretion of inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, induced by LPS stimulation in rat mesangial cells[19]. A similar decrease was detected for prostaglandin E2 (PGE2) and nitric oxide (NO), due to cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) inhibition by ALA pre-treatment[19]. Furthermore, ALA inhibits the expression of the inflammatory cytokine IL-8[20] and enhances IL-10 mRNA[21]. Moreover, recent clinical trials strengthened ALA profile as an effective immunomodulatory molecule to counteract some inflammatory disorders during pregnancy. Porcaro et al[22] carried out a randomized controlled clinical trial in pregnant women with threatened miscarriage. The study group was administered orally with ALA (600 mg/die) plus vaginal suppositories containing progesterone, whereas controls received only progesterone by vaginal route. The aim was to test the improvement of progesterone therapy for healing subchorionic hematomas and also for reducing subjective and objective signs such as vaginal bleeding, abdominal pain, and uterine contractions. The trial showed that ALA plus progesterone significantly improved the hematoma resorption compared to progesterone effect alone. In the study group was observed a faster reduction or disappearance of all symptoms in comparison to controls; however, such difference was not significant. Another controlled randomized clinical trial was carried out by Costantino et al[23] in women with threatened miscarriage to evaluate the effect of ALA (10 mg/die) or progesterone (control), both administered by vaginal route, in subchorionic hematoma resorption. In the treated group with ALA the subchorionic hematoma was significantly reabsorbed faster compared to the progression found in progesterone patients. Of note, a smaller number of miscarriages occurred in the ALA group compared to controls. Finally, a recent randomized clinical trial by Facchinetti et al[24], in women at risk of preterm labor, compared the effects of vaginal ALA (400 mg/die) to placebo. The authors demonstrated that the treatment significantly stimulated anti-inflammatory cytokines release in the cervix of patients at risk of PTB after primary tocolysis, and it was associated with a stabilization of the cervical length. All these effects agree with our results and give us a persuasive key of explanation. Obviously, our study has some evident limitations. The small sample reduces the power of the study weakening its promising results. The reduced incidence of this pathology, and consequently the low incidence of positive obstetric history of preterm birth, makes necessary the realization of a multicentre trial for the

collection of a suitable sample size. Our findings confirm the literature data with respect to tobacco smoke during pregnancy, and high BMI. In fact, smoking and obesity are related significantly to reduced treatment response and consequently increased risk of preterm delivery. Our study was the first one that evaluated the efficacy of the combination of ALA using together the oral and vaginal administration in women selected through cervicometry parameters, with or without symptoms, and monitored over time through transvaginal ultrasound which represents the most reliable, objective and reproducible measurement technique of the cervical canal.

CONCLUSIONS

This study demonstrated that the combined administration with ALA by oral and vaginal route obtained a statistically significant improvement of symptoms, with a reduced cervical shortening in patients at risk for preterm birth. The success of this new treatment in threatened preterm delivery would seem positively linked to a history of previous preterm birth, smoking and high maternal BMI. It is necessary to extend this study to a larger and randomized sample to confirm the therapy effectiveness.

Conflicts of interest:
The authors declare no conflicts of interest

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