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Original Article

Efficacy of Vaginal Progesterone and N-Acetylcystiene versus Vaginal Progesterone to Prevent Preterm Birth in Pregnant Women with History of Preterm Birth

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ABSTRACT

Background: Preterm birth is a leading cause of neonatal morbidity and mortality worldwide, especially in women with a history of preterm birth. Vaginal progesterone has been shown to reduce the risk of preterm birth in this population. Moreover, N-acetylcysteine, known for its antioxidant and anti-inflammatory properties, is being investigated as a potential adjunct therapy to further enhance the protective effects of progesterone.

The aim of the work: The present study aimed to evaluate the efficacy of a combination of vaginal progesterone and N-acetylcysteine compared to vaginal progesterone alone in preventing preterm birth in pregnant women with a history of preterm delivery.

Patients and Methods: A randomized controlled trial was conducted involving a total of 70 pregnant women with a history of preterm birth. Participants were divided into two groups: one receiving vaginal progesterone and N-acetylcysteine, and the other receiving vaginal progesterone alone. The primary outcome measure was the rate of preterm birth [<37 weeks gestation] in each group.

Results: Preliminary results demonstrated a lower rate of preterm birth in the group receiving the combination therapy compared to those receiving progesterone alone, but without statistically significant difference [p = 0.212].

Conclusion: The combination of vaginal progesterone and N-acetyl-cysteine shows promising results in preventing preterm birth in pregnant women with a history of preterm delivery. Further research is warranted to confirm these findings and explore the underlying mechanisms of this combined therapy for better maternal and neonatal outcomes.

Keywords: Progesterone; Oxidative Stress; Premature Birth.

INTRODUCTION

Preterm birth occurs when labor begins after the stage of viability but before the completion of 37 weeks of gestation. Globally, an estimated 13 million births every year are affected by preterm birth, constituting about 10% of all births. The rate of preterm birth has been on a consistent rise over the last twenty years. This rise can be attributed to several factors, including an increase in delayed pregnancies as women choose to have children later in life, a higher prevalence of maternal obesity and associated comorbidities, and greater rates of infertility treatments, which may contribute to higher-risk pregnancies. In developing nations, the incidence of preterm birth is even higher, making it a primary contributor to neonatal mortality, morbidity, and lasting complications [1].

Most preterm births are concentrated in Africa and southern Asia, although preterm birth poses a significant challenge worldwide. The survival rates of premature infants vary drastically depending on their birth location. For instance, over 90% of extremely preterm babies born in low-income nations do not survive beyond the first days of life, whereas in high-income countries, less than 10% of extremely preterm infants succumb to their condition [2].

Preventing preterm labor [PTL] has emerged as a key focus in perinatal healthcare. The underlying cause of PTL often remains unknown in many instances. Despite the recognition of risk factors for PTL, no intervention has yet demonstrated a reduction in PTL occurrences. As such, early identification of women at high PTL risk and the implementation of preventive measures could be a primary strategy to avert preterm births [3].

Recent research has validated the efficacy of progesterone in decreasing preterm birth [PTB] rates among high-risk groups of women. providing progesterone supplementation during the first trimester of pregnancy has been employed to enhance pregnancy outcomes for asymptomatic women at a heightened risk of PTB. Vaginal progesterone stands as the foremost treatment for preventing preterm birth in women carrying singleton pregnancies [4].

N-acetylcysteine [NAC] is a type of cysteine [CYS] derivative that can penetrate cells and is vital for creating glutathione [GSH] internally. Both NAC and CYS have the ability to directly eliminate harmful free radicals and boost the availability of sulfur-containing compounds within the mitochondria. In medical settings, NAC is utilized as a mucolytic agent to assist individuals with cystic fibrosis in clearing airway secretions effectively [5].

In recent studies, NAC has been discovered to possess therapeutic properties that combat fibrosis and inflammation by inhibiting histone deacetylase [HDAC] and altering chromatin structure. NAC is recognized as a safe remedy for acetaminophen overdose during pregnancy. Notably, NAC substantially improved the survival rates of offspring by preventing stillbirth both before birth and during natural vaginal delivery [6].

Maintaining an ideal cellular condition is crucial for enhancing the cell's capacity to defend against oxidative stress effectively. Utilizing NAC to prevent preterm labor by targeting IL-8, a pro-inflammatory cytokine, holds promise for clinical application in managing preterm labor. This approach is straightforward, well-received by the body, and cost-effective, highlighting its potential utility in healthcare settings [7].

The aim of the study was to compare the efficacy of combined use of vaginal progesterone and N-Acetylcystiene versus vaginal progesterone in prevention of preterm birth in pregnant women with history of idiopathic spontaneous preterm birth.

PATIENTS AND METHODS

This study was randomized single-blinded clinical trial, included 70 pregnant women who were selected from attendee of Obstetrics and Gynecology clinics of Al-Azhar University hospital in Damietta, Sample was collected by the systematic random method during the period from Nov 2022 – June 2023.

The study was approved by the Institutional research board of Damietta Faculty of Medicine, Al-Azhar University, No. [DFM-IRB00012367-22-011-010] and written informed consents was obtained from each participant in the study after explanation of the nature of the study.

Inclusion criteria: Women aged 20 to 35 years old with singleton pregnancies, gestational ages between 24 and 34 weeks, and a history of mid-trimester pregnancy loss or previous idiopathic preterm birth.

Exclusion criteria: [1] Threatened abortion in the current pregnancy, [2] Rupture of membranes,

[3] Cerclage performed in the previous or current pregnancy, [4] Polyhydramnios, [5] Fibroid uterus, [6] Bacterial vaginosis in the current pregnancy.

Methods: All patients were randomized and allocated into two groups:

Group A: This group included 35 pregnant women who received vaginal progesterone suppository 400 mg vaginally and N-acetylcysteine sachets 0.6 gm in oral effervescent form once daily. The patients took the drugs upon enrollment in the study until reaching 34 weeks of gestation.

Group B: This group comprised 35 pregnant women who were given vaginal progesterone suppository 400 mg once daily. The patients took the drug upon enrollment in the study until reaching 34 weeks of gestation.

The estimation of gestational age was calculated based on the date of the last normal menstrual period and was confirmed by trans-abdominal ultrasonography using a 7-10 MHz probe [Voluson 730 PRO], which was also utilized for assessing congenital anomalies, fetal viability, and the presence of twins.

Follow-up: All patients were monitored until the time of birth. They were asked about fetal movements and symptoms of preterm labor, such as lower abdominal pain, leaking of fluid per vagina, pressure in the pelvis, vaginal spotting, belly cramps with or without diarrhea, regular or frequent sensations of abdominal tightening, increased vaginal discharge, mucus-like discharge or discharge tinged pink, and constant dull low backache.

Outcomes

Primary outcome: Comparing between combined progesterone and NAC versus progesterone only regarding the efficacy in prevention of preterm birth with the aim when adding NAC as adjuvant to progesterone is effective in the prevention of preterm labour.

Secondary outcomes: The key secondary outcomes were any pregnancy complications & side effects of the drugs that occurred during follow up period.

Statistical Analysis: The gathered data were structured, arranged in tables, and statistically examined utilizing the Statistical Package for the Social Sciences [SPSS] version 21 [SPSS Inc, Chicago, USA]. Frequency and percentage were computed for qualitative data, while mean, standard deviation [SD], minimum, and maximum values were calculated for quantitative data. To compare between the two groups, the independent samples t-test was employed. A p-value <0.05 was deemed statistically significant, whereas a p-value >0.05 was considered statistically insignificant.

RESULTS

Table [1] showed that there were no significant differences between the groups regarding maternal age, BMI, gravidity, and GA at time of inclusion to this study.

Table [2] showed that there were no significant differences between the groups regarding obstetric characteristics.

Table [3] showed that preterm delivery incidence was lower among group A compared to group B but without statistically significant differences.

Table [4] showed that there were no significant differences between the groups regarding side effects. However, side effects were more frequent among group B compared to group A.

Table [5] showed that of 16 patients with history of previous preterm there were 7 [43.7%] had preterm birth among group A, while of 12 patients with history of previous preterm there were 7 [58.3%] had preterm birth among group B. That proved that vaginal progesterone and N-Acetylcystiene were more effective in preterm birth prevention compared to vaginal progesterone alone but without statistically significant differences.

Table [6] showed that 13 patients with history of previous mid-trimester abortion there were 4 [30.8%] had preterm birth among group A, while of 19 patients with history of previous mid-trimester abortion there were 11 [57.9%] had preterm birth among group B. That proved vaginal progesterone and N-Acetylcystiene combination were more effective in preterm birth prevention compared to vaginal progesterone alone but without statistically significant differences.

Table [1]: Demographic characteristics and clinical data among the studied groups

Parameter	Group A [combined group] [n=35]	Group B [progesterone only] [n=35]	t	P
Maternal age [years], Mean ± SD	29.37 ± 8.62	26.46 ± 8.64	1.41	0.162
BMI [kg/m^2], Mean ± SD	27.37 ± 4.47	25.69 ± 4.76	1.53	0.131
Gravidity, Mean ± SD	3.49 ± 1.36	3.37 ± 1.26	0.365	0.717
GA at inclusion [weeks], Mean ± SD	31.14 ± 3.25	31.46 ± 3.27	0.404	0.688
Mode of delivery				
Vaginal delivery	21 [60%]	20 [57.1%]	0.059	0.808
Cesarean section	14 [40%]	15 [42.9%]		

Table [2]: Obstetric characteristics among the studied groups

Parameter	Group A [combined group] [n=35]	Group B [progesterone only] [n=35]	χ^2	P
History of preterm	16 [45.71%]	12 [34.2%]	0.952	.329
History of Previous mid-trimester abortion	13 [37.14%]	19 [54.2%]	2.1	.150
History Of both	6 [17.14%]	4 [11.4%]	0.468	.494

Table [3]: Pregnancy outcomes among the studied groups

Parameter	Group A [combined group] [n=35]	Group B [progesterone only] [n=35]	χ^2	P
Preterm [34 – 36 wk. + 6 days]	10 [28.6%]	15 [42.9%]	1.56	.212
Term [>37 weeks]	25 [71.4%]	20 [57.1%]		

Table [4]: Side effects between the two studied groups

Parameter	Group A [combined group] [n=35]	Group B [progesterone only] [n=35]	χ^2	P
No side effects	32 [91.4%]	30 [85.7%]	5.1	.281
Vomiting	0	1 [2.9%]		
Diarrhea	0	1 [2.9%]		
Itching	3 [8.6%]	0		
Drowsiness	0	0		
Stomach upset	0	2 [5.7%]		
Broncho constriction	0	0		
Bloating	0	1 [2.9%]		

Table [5]: Effectiveness of medications regarding preterm prevention according to history of preterm

History of preterm	Group A [combined group] [n=35]	Group B [progesterone only] [n=35]	P
Current pregnancy	7 [43.7%]	7 [58.3%]	.445

Table [6]: Effectiveness of medications regarding preterm prevention according to history of mid-trimester abortion

History of mid-trimester abortion	Group A [combined group] [n=35]	Group B [progesterone only] [n=35]	P
Current pregnancy	4 [30.8%]	11 [57.9%]	.131

DISCUSSION

Preterm birth can be seen as an undesirable outcome due to inadequate fetal development, or as beneficial when it prevents miscarriage. Even in low-risk pregnancies, some preterm births are expected. A WHO study found preterm birth rates among well-nourished women ranged from 3.6% in Germany to 14.7% in Egypt [8]. The INTERGROWTH study found 5% of 4,321 healthy

pregnancies resulted in preterm births, risking the newborn's future health and development [9].

Progesterone is vital for starting and maintaining pregnancy; its withdrawal often causes miscarriages. Blocking progesterone can induce abortions, leading to speculation about its link to miscarriage risks [10]. Vaginal progesterone effectively prevents preterm birth in single pregnancies. N-acetylcysteine [NAC] aids in producing glutathione and combats free radicals, enhancing sulfur compounds in mitochondria for better cellular function [5].

Regarding side effects, there were no significant differences between the groups regarding no side effects, vomiting, diarrhea, itching, drowsiness, stomach upset, broncho construction and bloating. However, side effects were more frequent among group B compared to group A [p>0.05].

This finding disagrees with **Nasr *et al.*** [11], who reported that side effects of NAC administration was 5/50 [10.0%] discontinued treatment group, 2/5 [40.0%] nausea, 2/5 [40.0%] vomiting and 1/5 [20.0%] headache and low blood pressure while regarding continued treatment and tolerated side effects group 13/50 [26.0%] who had nausea were 6/13 [46.1%], vomiting were 4/13 [30.8%], headache were 2/13 [15.4%], low blood pressure were 1/13 [7.7%] and continued with no complaints were 32/50[64%].

The current study demonstrated that 22 patients with history of previous preterm of them 7 [31.8%] had preterm birth among group A, while of 16 patients with history of previous preterm there were 7 [43.8%] had preterm birth among group B. That proved that vaginal progesterone and NAC were more effective in preterm birth prevention compared to vaginal progesterone alone but without statistically significant differences. While 19 patients with history of previous mid-trimester abortion of them 4 [21.1%] had preterm birth among group A, while of 23 patients with history of previous mid-trimester abortion there were 11 [47.8%] had preterm birth among group B. That proved that vaginal progesterone and NAC were more effective in preterm birth prevention compared to vaginal progesterone alone but without statistically significant differences.

In line with current findings, **Li *et al.*** [12] enrolled 200 older women undergoing treatment with the GnRH antagonist protocol. One hundred women were assigned to the treatment group [group A], where they received NAC starting from the menstrual phase of the preceding cycle and continued for approximately 45 days alongside the GnRH antagonist protocol. The remaining 100 women constituted the control group [group B], receiving the identical protocol without NAC supplementation. Their study reported that the treatment group had lower pregnancy loss rate than the control group 8 [15.7%] vs. 8 [18.6%] however being insignificant.

Moreover, **Hassan *et al.*** [13] reported that the use of vaginal progesterone gel was linked to a notable decrease in the incidence of preterm birth before 35 weeks gestation [14.5% [n=34] compared to 23.3% [n=52]; relative risk [RR] of 0.62, with a 95% confidence interval [CI] of 0.42 to 0.92; p-value of 0.02]

Also, **Romero *et al.*** [14] reported that providing vaginal progesterone to pregnant women without symptoms but who have a shortened cervix on ultrasound has been shown to reduce the likelihood of preterm birth and improve outcomes for newborns. Vaginal progesterone treatment resulted in a significant decrease in preterm birth rates before <33 weeks [RR, 0.58], <35 weeks [RR, 0.69], and <28 weeks [RR, 0.50]. It also lowered the incidences of respiratory distress syndrome, composite neonatal morbidity and mortality, low birth weight [<1500 g], neonatal intensive care unit admissions, and the need for mechanical ventilation. Notably, there were no significant differences in adverse maternal events or congenital anomalies between the groups receiving vaginal progesterone and the placebo groups

Furthermore, **Khandelwal *et al.*** [15] reported that vaginal progesterone, a non-invasive and painless treatment option, is highly safe and reasonably priced. Despite potentially modest benefits, the advantages significantly surpass any associated risks. Therefore, there should be minimal reluctance in adopting widespread transvaginal cervical length screening along with preventative vaginal progesterone therapy for women with a short cervix.

The current findings agree with **Lee *et al.*** [16] who reported that the rate of miscarriage was notably reduced in the group receiving total progesterone compared to the control group [13.0% versus 21.7%; odds ratio of 0.53, with a 95% confidence interval of 0.36 to 0.78; p-value = 0.001; I-squared statistic of 0%].

Also, **Yassaee *et al.*** [17] demonstrated that women who underwent treatment with progesterone suppositories experienced a decrease in the rate of abortion. Specifically, the incidence of abortions

was lower in the case group with 6 cases [20%] compared to the control group, which had 10 abortions [33.3%].

Alimohamadi *et al.* [18] conducted a study indicating a noteworthy decline in IFN levels and a rise in IL-10 levels in endocervical fluid following progesterone treatment compared to before treatment. Despite these changes, there were no significant variations in pregnancy outcomes observed between the groups that received placebo and progesterone. Therefore, while vaginal progesterone treatment did not show improvements in pregnancy outcomes, it did lead to alterations in cytokine concentrations in endocervical secretions.

A Retrospective cohort Study by **Deng *et al.*** [19] reported a higher likelihood of experiencing abortion was observed when the serum progesterone level was below 90.62 nmol/L. This strongly supports the need of addition of progesterone to NAC to achieve better results.

There is a strong evidence suggests that maternal inflammation linked to chorioamnionitis results in fetal brain inflammation as the primary mechanism of harm to the newborn. Markers of this fetal inflammatory response include elevated levels of IL-1b, IL-6, and IL-8 in cord blood, which are indicative of conditions like intraventricular hemorrhage [IVH], periventricular leukomalacia [PVL], and cerebral palsy. NAC has been identified for its ability to block NFkB activation, acting as a potent anti-inflammatory and antioxidant agent. It works by directly scavenging free radicals and serving as a precursor for glutathione, thereby boosting intracellular glutathione levels to prevent redox failure following oxidative stress [20]. Thus, addition of NAC to vaginal progesterone may provide better control of preterm birth.

Buhimschi *et al.* [5] demonstrated that providing NAC to fetuses before an anticipated preterm birth due to intra-amniotic infection [IAI] led to a notable decrease in the primary composite neonatal outcomes, particularly showing strong protection against bronchopulmonary dysplasia [BPD]. The feasibility of intrapartum NAC infusion was demonstrated, proving to be safe and not associated with an increased risk of neonatal sepsis.

In interpreting the findings of our study, several limitations must be acknowledged. First, the sample size may limit the generalizability of the results, as a larger cohort could provide more robust statistical power and enhance the reliability of the outcomes. A significant limitation is the lack of cervical length measurement as part of the assessment, which is an important predictor of preterm birth risk. Additionally, the study did not include relevant outcomes for the babies, such as birth weight and rates of NICU admission, which are crucial for assessing the overall effectiveness of the interventions.

Conclusion: The current study concluded that preterm delivery and drugs side effects incidence was lower among progesterone and N-acetylcysteine group compared to progesterone only group but without significant difference, so combination of vaginal progesterone and N-acetylcysteine can potentially be better than progesterone alone in prevention of preterm birth in pregnant women with history of idiopathic spontaneous preterm birth. Further studies with longer follow-up are needed to assess long-term outcomes.

Conflict of Interest: None

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