

Efficacy of Vaginal Progesterone and Nifedipine in Inhibiting Threatened Preterm Labour

Aqdas Aziz, Uzma Riaz, Atiqa Noreen, Ishwa Iqbal

ABSTRACT:

Objective: To compare the effectiveness of vaginal progesterone and oral nifedipine in preventing threatened preterm labour.

Study design & Settings: randomized controlled trial (ClinicalTrials.gov Identifier: NCT07649668) that carried out a study in the Department of Gynecology, Hilal-e-Ahmar Hospital, Faisalabad

Methods: There were 160 pregnant women between 18 and 35 years old with a singleton pregnancy and the gestation age ranging 24 to 36 weeks, frequent painful uterine contractions, and cervical dilatation up to less than 2 cm. There was a random assignment of patients to two equal groups. Group A was given nifedipine, and Group B received vaginal micronized progesterone. The main outcome was efficacy, meaning the delayed delivery time beyond 48 hours of starting the therapy or the preterm birth not occurring within the time period. Data analysis was done with SPSS version 25.0 with a p-value of less than 0.05 and was taken as statistically significant.

Results: The study population had the mean age of 28.91+4.62 years and the mean gestational age of 32.84+2.71 weeks. In 59/80 patients, oral nifedipine was effective provided an efficacy rate of 73.75. In 72 out of 80 patients (efficacy of 90.00) vaginal progesterone proved to be effective. The difference of two groups was significant (p=0.008).

Conclusion: Oral nifedipine was less effective compared to vaginal progesterone in the inhibition of threatened preterm labour. It can be viewed as superior treatment modality in women having singleton pregnancy with threatened preterm labour.

Keywords: Threatened preterm labour, vaginal progesterone, nifedipine, tocolysis, preterm birth.

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INTRODUCTION:

Among the most hazardous problems that cannot be fully solved within the framework of the obstetrics is preterm birth that means the birth that takes place before 37 gestation weeks are completed. According to the latest world estimates, the percentage of the preterm born babies per year is approximately 13.4 million, which translates to almost 1 in ten live births around the world with the largest burden

being attributed to the South Asia and sub-Saharan Africa region.¹ Neonatal death, respiratory distress, sepsis, intraventricular bleeding, necrotizing enterocolitis, long-term neurodevelopmental disability, and significant economic/psychological burden to families and health systems are tightly interconnected with premature birth.^{1,2}

Threatened preterm labour is usually diagnosed when frequent uterine contractions end up at less than 37 gestation weeks and accompanied by minimal cervical dilation and intact membranes. Although not all of the women with symptoms will give birth to a preterm baby, it should be urgently evaluated because even several weeks of delayed delivery would mean the delivery of corticosteroids to the fetus as magnesium sulphate to preserve the fetus brain, use of antibiotics where appropriate and transfer to a hospital with a neonatal care unit.³ It is thus the explicit intention of the Tocolytic therapy not to cure but merely retard the pathological process to at least a 48 hours of birth.^{3,4}

One such widely used dihydropyridine calcium channel blocker is nifedipine, which is often used in acute tocolysis in the process of lowering calcium entry into the smooth-muscle cells of the uterus and consequently, decrease the uterine contractility. Systematic reviews have demonstrated that the calcium-channel blockers, especially nifedipine,

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are able to delay birth and have a favourable maternal adverse effect profile than a few older tocolytics.^{5,6} However, evidence-based on the matter is inconclusive, and some randomized trials have revealed weak nifedipine impacts on delivery at 48 hours, overall pre-term birth rate, neonatal consequences.^{7,8}

Progesterone is an exceedingly important hormone in sustaining pregnancy by improving myometrial quiescence, control of inflammatory pathways, and control of cervical and decidual activity.⁹ Vaginal progesterone has proven to be advantageous in preventing preterm birth in high-risk singleton pregnancies with presumably short cervix and meta-analyses of networks have established progesterone to be among the most suitable preventive measures in high-risk women.^{2,10} It possesses a local route of administration, a biological plausible and overall acceptable safety assessment which makes it an appealing option in women who present with threatened preterm labour.

Clinically, nifedipine and vaginal progesterone represent biologically and therapeutically different strategies. Nifedipine is used as an acute tocolytic to suppress uterine contractions for a short interval, whereas vaginal progesterone is better established as a preventive intervention for selected women at increased risk of spontaneous preterm birth, particularly those with a short cervix. Direct comparison in symptomatic threatened preterm labour is therefore not a comparison of interchangeable standard therapies, but a pragmatic evaluation of two approaches used in the local clinical setting. The clinically relevant question in this study was whether either assigned strategy was associated with a higher probability of avoiding delivery during the first 48 hours after treatment initiation, while recognizing that longer-term efficacy and safety require separate assessment.

Evidence directly comparing vaginal progesterone with oral nifedipine after the onset of symptomatic threatened preterm labour remains limited. This study therefore compared the two assigned strategies using a clearly defined 48-hour delivery-delay endpoint in a local hospital population. The study was not designed to establish that one intervention is generally superior for prevention of preterm birth across other populations or indications.

METHODOLOGY:

The study was a randomized controlled trial (ClinicalTrials.gov Identifier: NCT07649668) that carried out a study in the Department of Gynecology, Hilal-e-Ahmad Hospital, Faisalabad, upon an Institutional Ethical Review Committee approval (Ref No. 700/HAHF dated 20-08-2025). The research was conducted from 28th October 2025 to 27th April 2026. The aim of the research was to identify and compare the effectiveness of vaginal progesterone and oral nifedipine in preventing threatened preterm labour.

One hundred and sixty pregnant women meeting the selection criteria participated in the study. The level of significance,

power of study and the efficiency of oral nifedipine and vaginal progesterone expected were put at 73, 5, 90.5, respectively which were taken into the World Health Organization sample size calculator considering that 5 is the level of significance, 80 is the power of study, expected efficacy of oral nifedipine and vaginal progesterone. Eighty patients were included in each treatment group. Among the gynecology department, a non-probability consecutive sampling method was used to recruit the participants.

The study included pregnant women aged 18–35 years with a singleton pregnancy at 24–36 weeks who presented with threatened preterm labour, defined for study eligibility as regular painful uterine contractions (at least one every 10 minutes), intact membranes, and cervical dilatation <2 cm on vaginal examination before randomization. Women with cervical dilatation =2 cm at screening were therefore not eligible. Other exclusions were contraindication to either vaginal progesterone or oral nifedipine, gestational diabetes mellitus, gestational hypertension or preeclampsia, and multiple pregnancy. Cervical length measurement and fetal fibronectin testing were not incorporated into the recorded study eligibility or stratification variables; this limits risk stratification and comparison with short-cervix studies.

Each eligible participant received an explanation of the study purpose, procedures, potential benefits and confidentiality safeguards and provided written informed consent before randomization. Baseline demographic and obstetric data, including age, gestational age, height, weight, body mass index, socioeconomic status, residence, parity, and previous preterm birth, were recorded on a prespecified study proforma.

A computer-generated randomization sequence was used to allocate 160 participants in a 1:1 ratio to Group A (oral nifedipine) or Group B (vaginal micronized progesterone). The available study records identify computer-generated sequence allocation but do not document who generated the sequence, who enrolled participants, who assigned the interventions, or whether allocation was concealed using sequentially numbered opaque envelopes or central allocation. The interventions differed in route and schedule, so participant and treating-clinician blinding was not described and should not be assumed. Group A received oral nifedipine with an initial 20 mg dose repeated at 30-minute intervals for up to three doses, followed by sustained-release nifedipine 20 mg every 12 hours according to the study regimen. Group B received vaginal micronized progesterone 200 mg once daily. Treatment was continued according to the study protocol and clinical status.

The prespecified primary endpoint was short-term treatment success, defined as the participant remaining undelivered for at least 48 hours after initiation of the assigned treatment. Delivery at any time within 48 hours was classified as primary-endpoint failure. The previous wording that

combined “delay beyond 48 hours” with “absence of preterm birth during the observation period” has been removed because these are not equivalent outcomes. Longer-term outcomes such as gestational age at delivery, total latency to delivery, birth before 37 weeks, neonatal morbidity and mortality, and readmission were not part of the primary endpoint and were not systematically available in the study dataset. Clinical monitoring during the initial treatment period included uterine contractions, cervical change, membrane rupture, need for additional obstetric intervention, and delivery status.

Data were analyzed using SPSS version 25. Continuous baseline variables were summarized as mean $\pm$ standard deviation and compared between treatment groups using independent-samples t-tests. Categorical variables were summarized as frequency and percentage and compared using Pearson chi-square tests; Fisher exact testing was appropriate when expected cell counts were small. The primary analysis followed the randomized groups and included all 160 participants (80 per group) for whom the primary 48-hour endpoint was reported, consistent with an intention-to-treat approach for the primary endpoint. The primary treatment effect was reported as the risk ratio and absolute risk difference with 95% confidence intervals in addition to the two-sided Pearson chi-square p-value. Prespecified subgroup comparisons by age, parity, gestational age, body mass index, socioeconomic status, residence, and previous preterm birth were treated as exploratory. No formal treatment-by-subgroup interaction tests or multiplicity adjustment were performed; therefore, subgroup-specific p-values were not interpreted as evidence of differential treatment effect. A two-sided p-value <0.05 was considered statistically significant for the primary comparison.

RESULTS:

The mean maternal age was 28.91 ± 4.62 years, mean gestational age at presentation was 32.84 ± 2.71 weeks, and mean body mass index was 25.78 ± 3.41 kg/m². Baseline continuous characteristics were similar between randomized groups; however, absence of a statistically significant difference should not be interpreted as proof of equivalence.

In Group A, the mean age was 28.72 ± 4.51 years, while in Group B it was 29.10 ± 4.74 years. Mean gestational age of the nifedipine group was 32.68 ± 2.83 weeks and progesterone group had 33.01 ± 2.58 weeks. The mean body mass index was 25.62 ± 3.36 kg/m² in Group A and 25.94 ± 3.47 kg/m² in Group B. The differences between the ages of the two groups, their gestational ages, their height, weight, and their BMI were not statistically significant.

Baseline categorical characteristics were also similar between groups. Group A included 42 urban and 38 rural participants, while Group B included 45 urban and 35 rural participants. Primigravida participants numbered 31 in Group A and 29 in Group B. Previous preterm birth was reported by 18

participants in Group A and 20 in Group B. No statistically significant baseline differences were detected for socioeconomic status, residence, parity, or previous preterm birth.

The prespecified primary endpoint was remaining undelivered for at least 48 hours after treatment initiation. This endpoint was achieved by 59/80 women (73.75%) assigned to oral nifedipine and 72/80 women (90.00%) assigned to vaginal progesterone (Pearson chi-square $p=0.008$). The risk ratio for 48-hour treatment success with vaginal progesterone versus nifedipine was 1.22 (95% CI 1.05–1.42), and the absolute risk difference was 16.25 percentage points (95% CI 4.58–27.92). All 160 randomized participants were included in the reported primary analysis according to assigned treatment group. The dataset did not separately document adherence/compliance, treatment discontinuation, protocol deviation, crossover, rescue tocolysis, maternal adverse effects, additional obstetric interventions, gestational age at delivery, total latency to delivery, or neonatal outcomes.

Exploratory subgroup comparisons were performed according to maternal age, gestational age, body mass index, parity, socioeconomic status, residence, and previous preterm birth. Some within-stratum comparisons had p-values <0.05 ; however, no treatment-by-subgroup interaction tests were performed and no adjustment was made for multiple comparisons. These analyses therefore should be interpreted as exploratory only and do not establish subgroup-specific superiority of either intervention.

Overall, the randomized comparison showed a higher 48-hour treatment-success proportion in the vaginal progesterone group than in the nifedipine group. This finding applies to the prespecified short-term endpoint in this study population and does not by itself establish superiority for longer-term prevention of preterm birth, maternal safety, or neonatal outcomes.

Figure 1. CONSORT-style participant flow for the randomized analysis

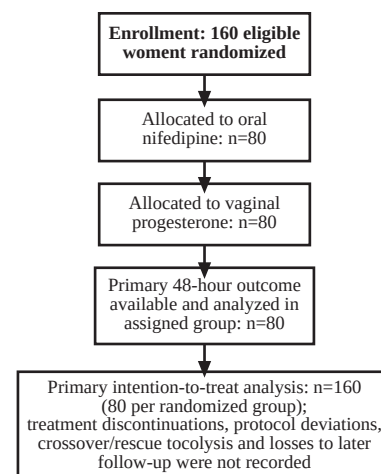


Table 1. Baseline quantitative characteristics of study participants

Variable	Group A: Oral Nifedipine n=80 Mean $\pm$ SD	Group B: Vaginal Progesterone n=80 Mean $\pm$ SD	p-value
Age, years	28.72 $\pm$ 4.51	29.10 $\pm$ 4.74	0.604
Gestational age, weeks	32.68 $\pm$ 2.83	33.01 $\pm$ 2.58	0.443
Weight, kg	67.84 $\pm$ 8.92	68.21 $\pm$ 9.14	0.796
Height, m	1.62 $\pm$ 0.06	1.63 $\pm$ 0.05	0.253
BMI, kg/m ²	25.62 $\pm$ 3.36	25.94 $\pm$ 3.47	0.554

Table 2. Baseline categorical characteristics of study participants

Variable	Group A: Oral Nifedipine n=80	Group B: Vaginal Progesterone n=80	p-value
Socioeconomic status			
Lower	25 (31.25%)	23 (28.75%)	0.841
Middle	42 (52.50%)	44 (55.00%)	
Higher	13 (16.25%)	13 (16.25%)	
Residence			
Rural	38 (47.50%)	35 (43.75%)	0.632
Urban	42 (52.50%)	45 (56.25%)	
Parity			
Primigravida	31 (38.75%)	29 (36.25%)	0.742
Multigravida	49 (61.25%)	51 (63.75%)	
Previous preterm delivery			
Yes	18 (22.50%)	20 (25.00%)	0.715
No	62 (77.50%)	60 (75.00%)	

Table 3. Comparison of efficacy between oral nifedipine and vaginal progesterone

Efficacy	Group A: Oral Nifedipine n=80	Group B: Vaginal Progesterone n=80	Total	p-value
Yes	59 (73.75%)	72 (90.00%)	131 (81.88%)	0.008
No	21 (26.25%)	8 (10.00%)	29 (18.12%)	
Total	80 (100.00%)	80 (100.00%)	160 (100.00%)	

Primary treatment effect (vaginal progesterone vs oral nifedipine): risk ratio 1.22 (95% CI 1.05–1.42); absolute risk difference 16.25 percentage points (95% CI 4.58–27.92). Pearson chi-square $p=0.008$. Analysis included all 160 randomized participants in their assigned groups.

Table 4. Exploratory subgroup comparison of 48-hour treatment success according to maternal and obstetric variables

Stratification variable	Group A effective / total	Group A efficacy	Group B effective / total	Group B efficacy	p-value
Age 18–25 years	22/30	73.33%	25/28	89.29%	0.125
Age 26–35 years	37/50	74.00%	47/52	90.38%	0.030
Gestational age 24–30 weeks	18/25	72.00%	22/26	84.62%	0.279
Gestational age 31–36 weeks	41/55	74.55%	50/54	92.59%	0.013
BMI $\leq$ 25 kg/m ²	27/38	71.05%	36/40	90.00%	0.036
BMI $>$ 25 kg/m ²	32/42	76.19%	36/40	90.00%	0.102
Primigravida	22/31	70.97%	25/29	86.21%	0.151
Multigravida	37/49	75.51%	47/51	92.16%	0.024

Table 5. Exploratory subgroup comparison of 48-hour treatment success according to residence, socioeconomic status, and previous preterm delivery

Stratification variable	Group A effective / total	Group A efficacy	Group B effective / total	Group B efficacy	p-value
Rural residence	27/38	71.05%	31/35	88.57%	0.064
Urban residence	32/42	76.19%	41/45	91.11%	0.056
Lower socioeconomic status	18/25	72.00%	20/23	86.96%	0.201
Middle socioeconomic status	31/42	73.81%	40/44	90.91%	0.036
Higher socioeconomic status	10/13	76.92%	12/13	92.31%	0.271
Previous preterm delivery: Yes	12/18	66.67%	17/20	85.00%	0.181
Previous preterm delivery: No	47/62	75.81%	55/60	91.67%	0.019

Note: Subgroup analyses are exploratory. No formal interaction testing or multiplicity correction was performed; individual subgroup p-values should not be interpreted as evidence that treatment effects differ across subgroups

DISCUSSION:

The principal finding was that 90.0% of women assigned to vaginal progesterone and 73.75% assigned to oral nifedipine remained undelivered for at least 48 hours after treatment initiation. The corresponding risk ratio was 1.22 (95% CI 1.05–1.42) and the absolute risk difference was 16.25 percentage points (95% CI 4.58–27.92). This comparison addresses a short-term delivery-delay endpoint only. It should not be interpreted as evidence that vaginal progesterone is generally superior to nifedipine for prevention of preterm birth, because the interventions have different established clinical roles and longer-term obstetric, neonatal, adherence, rescue-treatment, and safety outcomes were not comprehensively captured.

Vaginal progesterone has an established preventive role in selected high-risk singleton pregnancies, particularly in women with a short cervix, whereas nifedipine is used for acute tocolysis.¹¹ These differences are important when interpreting the present pragmatic comparison in symptomatic threatened preterm labour. The current study did not measure cervical length or fetal fibronectin and therefore cannot determine whether the observed 48-hour difference was concentrated among women with a sonographically short cervix or another specific risk phenotype. Current results were as well compared with reports of progesterone in high-risk women. Conde-Agudelo and Romero found that vaginal progesterone consistently prevented repeated preterm birth in no women with a history of spontaneous preterm birth, although it was more beneficial in the presence of cervical shortening.¹² This suggests that patient selection is important. Women with symptomatic threatened preterm labour were featured in our study and progesterone perhaps was most effective in those where the cervical changes had not so far reached up. This is justified by the fact that the study operational definition of threatened preterm labour was the cervical dilatation of less than 2 cm.

The 73.75% 48-hour success proportion in the nifedipine group is consistent with its role as an acute tocolytic intended to provide a short interval for antenatal corticosteroids, fetal

neuroprotection when indicated, and transfer to an appropriate neonatal facility.¹³ The present study did not evaluate whether either treatment improved gestational age at delivery or neonatal outcomes, so the short-term endpoint should not be extrapolated to longer-term perinatal benefit.

Recent test studies involving other cervical and hormonal treatments also endorse the relevance of progesterone as a therapeutics of clinical use. BMJ randomized trial by van Dijk et al. compared cervical pessary with vaginal progesterone in singleton pregnancy with a short cervix, and no prior spontaneous preterm births before 34 weeks of gestation and did not demonstrate any difference between cervical pessary and vaginal progesterone.¹⁴ Likewise, Chau et al. found cervical pessary inferior to vaginal progesterone in singleton pregnancies with short cervix.¹⁵ These analyses reinforce the meaning that progesterone will still be a reasonable choice among high-risk patients who are chosen under the objective of preventing preterm birth but not with mechanical cervical support. We also used comparative data with combined approaches which supported our findings. It was also observed that the use of combined vaginal progesterone and cervical cerclage can minimize preterm birth in comparison with any one of the two interventions in specific patients.¹⁶ Nevertheless, according to the study by Pacagnella et al., the introduction of pessary with progesterone did not show significant differences with progesterone in terms of morbidity and mortality in infants.¹⁷ These results indicate progesterone might play the role of central useful intervention, and the addition of mechanical interventions should be based on the patient group, cervical results, and the history of obstetric. The randomized groups had similar measured baseline characteristics. Exploratory subgroup analyses suggested numerical differences in several strata, but these analyses were not supported by formal interaction testing and were not adjusted for multiple comparisons. Therefore, the study does not establish that age, gestational age, BMI, parity, socioeconomic status, residence, or previous preterm birth modifies the comparative treatment effect.

Gestational-age subgroup findings should be regarded as exploratory. Although the 31–36-week stratum showed a nominally significant within-stratum comparison, no interaction test demonstrated that the treatment effect differed by gestational age. In addition, cervical length and fetal fibronectin were not measured, limiting clinical risk stratification and mechanistic interpretation. Parity subgroup findings were also exploratory. A nominal within-stratum p-value in multigravida women does not establish treatment-effect modification because interaction testing was not performed. Larger trials should prospectively evaluate whether parity, cervical length, previous spontaneous preterm birth, and other baseline risk factors modify response. The analysis among women with and without previous preterm birth was exploratory. The study was not powered for subgroup interaction testing, and no conclusion of subgroup-specific superiority should be drawn. Future trials should prespecify subgroup hypotheses and incorporate objective cervical assessment and longer-term delivery outcomes.

In recent twin-pregnancy trials and meta-analyses, the effects of progesterone and mechanical interventions vary more. He et al. compared cerclage and pessary, including vaginal progesterone in pregnancies with short cervix in twins and discovered that relative advantage of interventions was complicated.¹⁸ D'Antonio et al. also provided inconsistent results with respect to progesterone, cerclage and pessary use in twin pregnancies.¹⁹ As the current research involved only singleton pregnancies the results could be better applied to singleton threatened preterm labour and should not be extrapolated to twins. Avoiding delivery during the first 48 hours can be clinically important because it may allow time for antenatal corticosteroids, magnesium sulfate for fetal neuroprotection when indicated, and transfer to a facility with appropriate neonatal care.²⁰ However, this study did not systematically capture corticosteroid completion, rescue tocolysis, additional obstetric interventions, gestational age at delivery, total latency, maternal adverse effects, or neonatal outcomes. Consequently, the findings are limited to the prespecified 48-hour endpoint and cannot determine comparative safety or downstream neonatal benefit.

CONCLUSION:

In this single-center randomized study, a greater proportion of women assigned to vaginal micronized progesterone than to oral nifedipine remained undelivered for at least 48 hours after treatment initiation (90.0% vs 73.75%; RR 1.22, 95% CI 1.05–1.42). The result supports a difference in the prespecified short-term endpoint within this study population, but it does not establish general superiority of vaginal progesterone for prevention of preterm birth. Confirmation requires larger trials that assess adherence, rescue treatment, maternal adverse effects, gestational age and latency to delivery, and clinically relevant neonatal outcomes.

Limitations: This was a single-center study, which limits generalizability. Although computer-generated randomization was reported, the available records did not document who generated the sequence, who enrolled or assigned participants, whether allocation concealment was used, or whether any outcome assessor was blinded. The number screened and excluded before randomization was not retained. Cervical length and fetal fibronectin were not recorded for risk stratification. All 160 randomized participants were included in the reported 48-hour primary analysis, but treatment adherence, discontinuation, protocol deviations, crossover or rescue tocolysis, maternal adverse effects, additional obstetric interventions, gestational age at delivery, total latency to delivery, and neonatal outcomes were not systematically available. Therefore, comparative safety and longer-term efficacy cannot be determined. Subgroup analyses were exploratory, were not adjusted for multiplicity, and did not include formal interaction testing. These limitations should be addressed in a larger multicenter randomized trial with concealed allocation, prespecified follow-up windows, comprehensive safety reporting, and neonatal follow-up.

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Authors Contribution:

Aqdas Aziz: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Uzma Riaz: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Atiqa Noreen: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Ishwa Iqbal: Conception and Design, acquisition of data, drafting and critical revision, final approval of the version to be published

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