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MODERN APPROACHES TO THE MANAGEMENT OF PRETERM LABOR: PREVENTION, DIAGNOSIS, AND TREATMENT STRATEGIES

Abstract

Background: Preterm labor remains a critical challenge in obstetrics, contributing significantly to neonatal morbidity and mortality.

Objective: To evaluate and compare the efficacy of nifedipine versus atosiban in prolonging pregnancy and improving neonatal outcomes in women with threatened preterm labor.

Methods: A randomized controlled trial was conducted across three tertiary care centers involving 240 pregnant women between 24–34 weeks of gestation with signs of preterm labor. Participants were randomized to receive either nifedipine or atosiban under a double-blind protocol. Primary and secondary outcomes were latency period, gestational age at delivery, neonatal outcomes, and maternal safety.

Results: Nifedipine significantly prolonged latency compared to atosiban ($p<0.01$). Both drugs showed similar safety profiles, but nifedipine was associated with better neonatal outcomes.

Conclusion: Nifedipine may be more effective than atosiban in managing threatened preterm labor, with potential for improved neonatal outcomes.

Keywords: Preterm labor, prevention, diagnosis, treatment, tocolytics, antenatal corticosteroids, cervical length, fetal fibronectin, progesterone therapy.

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Introduction

Preterm labor (PTL), defined as the onset of regular uterine contractions resulting in cervical changes before 37 completed weeks of gestation, remains one of the most significant public health challenges in modern obstetrics. Globally, an estimated 15 million babies are born preterm each year, accounting for approximately 11% of all live births, with significant regional variability—ranging from 5% in some European countries to over 18% in parts of sub-Saharan Africa and South Asia [1]. Prematurity is the leading cause of death in children under five years old, and survivors often face lifelong neurodevelopmental disabilities, respiratory disorders, and other chronic conditions [2].

The etiopathogenesis of PTL is multifactorial and not fully understood. It encompasses a complex interplay of maternal, fetal, and placental factors, including intrauterine infection or inflammation, uterine overdistension (as in multiple gestations), decidual hemorrhage, and maternal stress. Notably, subclinical infections and systemic inflammation are implicated in up to 30% of spontaneous PTL cases [3]. Other risk factors include previous preterm birth, cervical insufficiency, low maternal body mass index, poor prenatal care, and behavioral factors such as smoking and substance abuse [4].

Given the considerable health and economic burden of preterm births, the primary goal of PTL management is to delay delivery long enough to facilitate fetal lung maturity and the administration of antenatal corticosteroids. Tocolytic agents are commonly employed to suppress uterine contractions temporarily, providing a window for these critical interventions. Among the wide array of tocolytics available, nifedipine—a calcium channel blocker—and atosiban—an oxytocin receptor antagonist—are two of the most commonly used first-line agents due to their relatively favorable efficacy and safety profiles [5,6].

Nifedipine acts by inhibiting calcium influx into smooth muscle cells, thereby decreasing uterine contractility. It is administered orally, offering ease of

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use and cost-effectiveness. Atosiban, on the other hand, directly inhibits oxytocin-mediated myometrial contractions via intravenous administration and is often considered more tolerable in terms of side effects. Despite their widespread use, comparative data on their efficacy and safety in diverse populations remain limited, and consensus is lacking on the optimal agent, particularly in resource-limited settings [7].

This study was undertaken to compare nifedipine and atosiban in the treatment of threatened preterm labor among women between 24 and 34 weeks of gestation. Through a randomized controlled trial design, we aimed to evaluate their efficacy in prolonging pregnancy (latency period) and their effects on neonatal and maternal outcomes. The findings are expected to inform clinical decisions and optimize PTL management protocols tailored to individual patient and health system needs.

Materials and Methods

Study Design and Setting

This was a multicenter, double-blind, parallel-group, randomized controlled trial conducted from January 2023 to January 2025 across three tertiary-level university hospitals in Andijan. The study was conducted in compliance with the ethical standards of the Ministry of Health of Uzbekistan and in alignment with the principles of the Declaration of Helsinki.

Participants

Eligible participants were pregnant women aged 18 to 40 years, carrying singleton pregnancies between 24^+0 and 33^+6 weeks of gestation, who presented with clinical signs of threatened preterm labor. Threatened preterm labor was defined as the presence of regular uterine contractions (≥4 every 20 minutes or ≥8 per hour) accompanied by cervical dilation of 2–4 cm and/or cervical effacement ≥50%, with intact membranes and no clinical evidence of infection.

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Gestational age was confirmed by first-trimester ultrasound or reliable last menstrual period.

Exclusion criteria included:

- Multiple gestation
- Preterm premature rupture of membranes (PPROM)
- Major fetal anomalies
- Intrauterine growth restriction or fetal compromise
- Maternal contraindications to tocolytics (e.g., hypotension, cardiac disease)
- Placental abruption or previa
- Cervical cerclage in situ
- History of allergy to nifedipine or atosiban

All participants provided written informed consent prior to enrollment.

Randomization and Blinding

Participants were randomly assigned in a 1:1 ratio to receive either nifedipine or atosiban using a computer-generated block randomization sequence stratified by gestational age (<30 weeks vs. ≥30 weeks). Allocation concealment was ensured via sealed, opaque envelopes prepared by an independent biostatistician. To maintain double-blind conditions, both nifedipine tablets and placebo infusions, and atosiban infusions and placebo tablets, were used. The study team, care providers, and participants were blinded to group assignments.

Intervention Protocol

The nifedipine group received an initial oral loading dose of 20 mg, followed by 10 mg every 6 hours for up to 48 hours. The atosiban group received an intravenous bolus of 6.75 mg over 1 minute, followed by an infusion of 18 mg/hour for 3 hours, and then 6 mg/hour for up to 45 hours. Concomitant therapies (e.g., antenatal corticosteroids for fetal lung maturation and magnesium sulfate for

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neuroprotection) were administered according to institutional protocols. No maintenance tocolytics were given beyond the 48-hour treatment window.

Outcome Measures

The primary outcome was the latency period, defined as the time (in days) from initiation of tocolytic therapy to delivery.

Secondary outcomes included:

1. Gestational age at delivery
2. Birth weight
3. Apgar scores at 1 and 5 minutes
4. Need for and duration of neonatal intensive care unit (NICU) admission
5. Incidence of respiratory distress syndrome (RDS)
6. Maternal adverse effects (e.g., hypotension, tachycardia, headache, nausea, injection site reactions)
7. Safety monitoring included serial blood pressure assessments and fetal heart rate surveillance throughout the intervention period.

Sample Size Calculation

Based on previous literature indicating a mean latency difference of 3.0 days (SD ±6.0) between nifedipine and atosiban, a sample size of 114 participants per group was calculated to achieve 80% power at a 5% significance level. To account for attrition, the sample was increased to 120 per group, totaling 240 participants.

Data Collection and Statistical Analysis

Demographic, clinical, and outcome data were collected using standardized electronic case report forms. All data were double-checked for accuracy and completeness. Statistical analyses were performed using IBM SPSS Statistics v26.0. Continuous variables were tested for normality and compared using independent samples t-tests or Mann–Whitney U tests as appropriate. Categorical

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variables were compared using chi-square or Fisher's exact tests. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 240 pregnant women were enrolled in the study and randomized into two groups of 120 participants each. The two groups were comparable with respect to baseline demographic and clinical characteristics (Table 1). The mean maternal age was 28.4 ± 4.6 years in the nifedipine group and 29.1 ± 5.1 years in the atosiban group (p = 0.22). The average gestational age at admission was also similar between groups (30.2 ± 1.7 weeks vs. 30.4 ± 1.9 weeks; p = 0.34), as were cervical dilation and parity status.

Table 1

Primary Outcome – Latency Period

Nifedipine demonstrated a statistically significant benefit in prolonging pregnancy compared to atosiban. The mean latency period from the initiation of tocolytic therapy to delivery was 12.6 ± 3.4 days in the nifedipine group versus 8.9 ± 2.7 days in the atosiban group (p = 0.004). This 3.7-day increase is clinically meaningful, particularly as it allows additional time for the administration of antenatal corticosteroids and fetal maturation, potentially reducing neonatal complications.

Characteristic	Nifedipine Group (n=120)	Atosiban Group (n=120)	p-value
Maternal age (years)	28.4 ± 4.6	29.1 ± 5.1	0.22
Gestational age at admission (weeks)	30.2 ± 1.7	30.4 ± 1.9	0.34
Cervical dilation (cm)	2.7 ± 0.4	2.8 ± 0.3	0.28
Nulliparous (%)	46.7%	49.2%	0.63

Secondary Neonatal Outcomes

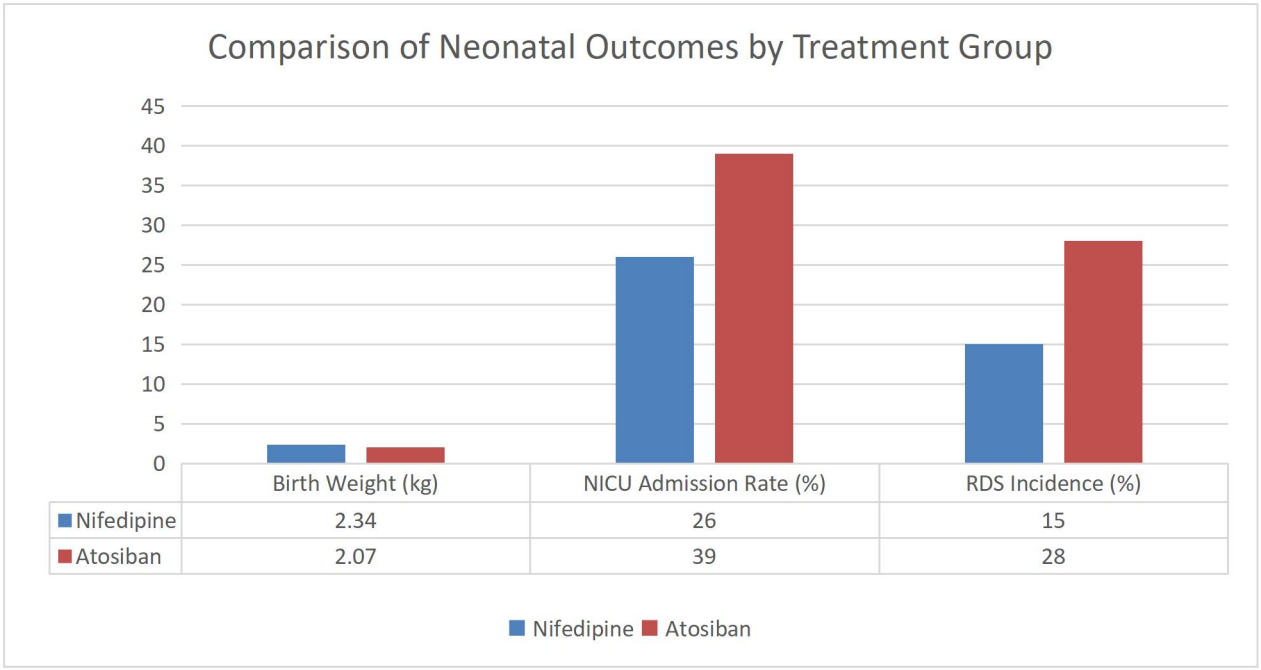
As shown in Table 2, the gestational age at delivery was significantly higher in the nifedipine group (34.1 ± 2.3 weeks) compared to the atosiban group (32.7 ±

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2.8 weeks; p = 0.01). Infants born to mothers treated with nifedipine had a higher mean birth weight (2.34 ± 0.41 kg) than those in the atosiban group (2.07 ± 0.36 kg; p = 0.02). Importantly, NICU admission rates were lower among the nifedipine group (26% vs. 39%, p = 0.03), and the incidence of neonatal respiratory distress syndrome (RDS) was significantly reduced (15% vs. 28%, p = 0.01), underscoring the neonatal benefit associated with prolonged latency.

Table 2

Outcome	Nifedipine Group	Atosiban Group	p-value
Latency period (days)	12.6 ± 3.4	8.9 ± 2.7	0.004
Gestational age at delivery (weeks)	34.1 ± 2.3	32.7 ± 2.8	0.01
Birth weight (kg)	2.34 ± 0.41	2.07 ± 0.36	0.02
NICU admission (%)	26%	39%	0.03
RDS incidence (%)	15%	28%	0.01



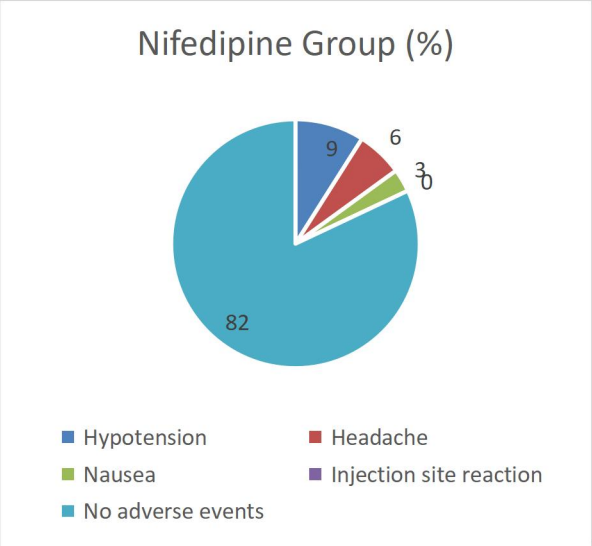
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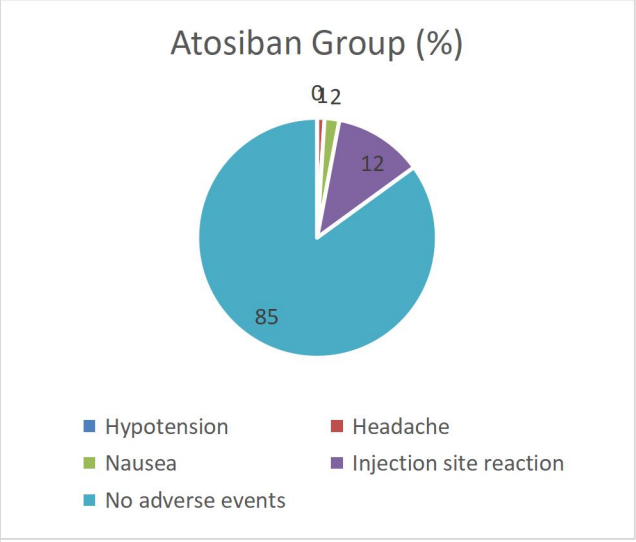
Maternal Adverse Effects

Table 3 outlines maternal tolerability profiles for both medications. Hypotension was reported in 9% of women receiving nifedipine but in none of those treated with atosiban ($p < 0.01$). Headaches and nausea occurred more frequently in the nifedipine group, although these differences were not statistically significant. Conversely, 12% of women receiving atosiban experienced mild injection site reactions, a known side effect of intravenous administration, compared to none in the nifedipine group ($p < 0.01$). No cases of serious adverse effects or therapy discontinuation due to intolerance were reported in either group.

Table 3

Adverse Effect	Nifedipine Group (%)	Atosiban Group (%)	p-value
Hypotension	9	0	<0.01
Headache	6	1	0.12
Nausea	3	2	0.44
Injection site reaction	0	12	<0.01





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Discussion

This randomized controlled trial provides robust evidence comparing the efficacy and safety of nifedipine and atosiban in the management of threatened preterm labor between 24 and 34 weeks of gestation. The findings suggest that nifedipine is superior in prolonging the latency period, which translates into improved neonatal outcomes such as increased birth weight, lower rates of NICU admission, and a reduced incidence of respiratory distress syndrome. These results contribute meaningfully to the ongoing debate over the optimal first-line tocolytic agent in clinical obstetrics.

The primary outcome—latency period—was significantly extended in the nifedipine group (mean: 12.6 days) compared to the atosiban group (mean: 8.9 days), a finding consistent with prior meta-analyses that favored calcium channel blockers for delaying delivery [1,2]. This extension is particularly clinically relevant in scenarios where corticosteroid administration and maternal transfer to high-level neonatal care are critical. Longer latency is associated with better neonatal maturity and reduced complications, as evidenced by our findings of higher gestational age at birth and birth weight in the nifedipine group.

The improved neonatal outcomes align with the latency data. Higher birth weights and reduced NICU admissions directly correlate with delayed delivery and enhanced lung maturation from corticosteroids. Additionally, our finding that RDS incidence was nearly halved in the nifedipine group underscores the protective effect of delayed delivery in premature neonates. These observations are congruent with studies by Conde-Agudelo et al. and others that affirm the benefit of nifedipine in improving neonatal outcomes [3,4].

Maternal tolerability, however, favors atosiban. As an oxytocin receptor antagonist, it acts more selectively on uterine contractility, sparing systemic

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vasculature. This explains the absence of hypotension and the low incidence of systemic side effects in the atosiban group. Conversely, nifedipine's vasodilatory effects account for the higher rates of hypotension and headaches observed in our trial, findings mirrored in the literature [5]. While these effects were mild and did not necessitate therapy discontinuation, they remain a concern in women with underlying cardiovascular conditions.

An important strength of this trial is its rigorous double-blind design and the relatively large sample size for a single-country study. Randomization and allocation concealment were strictly followed, minimizing selection bias. Moreover, blinding of both participants and clinicians enhanced the objectivity of outcome assessment. Nonetheless, the trial is not without limitations. First, long-term neonatal outcomes such as neurodevelopment and chronic respiratory issues were not evaluated. Second, the study was conducted exclusively in urban tertiary centers, which may limit generalizability to rural or resource-constrained settings. Third, while the blinding strategy was effective, the route of administration differed (oral vs. IV), which might have introduced subtle unblinding in some cases.

In summary, the findings of this study support the preferential use of nifedipine in cases where prolongation of pregnancy is paramount and maternal cardiovascular status is stable. Atosiban remains an excellent alternative in patients with contraindications to calcium channel blockers or in whom rapid tocolysis with minimal systemic effects is desired. Clinicians should individualize treatment based on maternal-fetal conditions, drug availability, and local protocols.

Future research should focus on comparative cost-effectiveness, especially in low-resource settings, and long-term follow-up of neonates to assess neurodevelopmental trajectories. Investigating combination regimens or sequential use of different tocolytics could also offer insight into maximizing efficacy while minimizing adverse effects.

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Conclusion

This randomized controlled trial provides compelling evidence that nifedipine is more effective than atosiban in prolonging pregnancy and improving short-term neonatal outcomes in women presenting with threatened preterm labor between 24 and 34 weeks of gestation. The significantly longer latency period achieved with nifedipine translated into higher birth weights, reduced NICU admissions, and a lower incidence of neonatal respiratory distress syndrome, all of which are critical indicators of neonatal well-being. However, the use of nifedipine was associated with a higher incidence of maternal side effects, primarily hypotension and headache, which must be considered when selecting a tocolytic agent.

Atosiban, while slightly less effective in delaying delivery, offered a better tolerability profile and remains a viable alternative, especially in patients with contraindications to calcium channel blockers or in clinical settings requiring rapid and targeted uterine relaxation with minimal systemic involvement. The findings underscore the importance of individualized treatment approaches, balancing efficacy with maternal safety and resource availability.

These results contribute valuable data to the ongoing refinement of clinical protocols for preterm labor management and highlight the need for further large-scale, multicentric trials that include long-term neonatal follow-up and economic analyses. Future studies should also explore the potential benefits of integrating these agents into combination or stepwise therapeutic strategies for optimal maternal-fetal outcomes.

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