International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Dewan B et al. Int J Reprod Contracept Obstet Gynecol. 2024 Nov;13(11):3420-3431
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20243223

Review Article

Atosiban: a comprehensive approach to preterm labour management

Bhupesh Dewan*, Sanjaykumar Navale, Rishima Ganiga

Department of Medical Services, Zuventus Healthcare Limited, Mumbai, Maharashtra, India

Received: 29 August 2024
Accepted: 04 October 2024

***Correspondence:**
Dr. Bhupesh Dewan,
E-mail: bhupesh.dewan@zuventus.com

ABSTRACT

Preterm birth (PTB) continues to be a leading cause of neonatal mortality and long-term complications globally, reinforcing the need for effective and safe tocolytic treatments. Atosiban, an oxytocin receptor antagonist, has emerged as a pivotal intervention for managing spontaneous preterm labour (sPTL) due to its targeted mechanism and favourable safety profile. This is especially critical in regions like India, where there is a significant therapeutic gap in the availability of effective, safe, and cost-efficient tocolytic agents. Dosing regimens for Atosiban include a full course (48 hours), a brief course (14 hours), and a single bolus dose. The brief and bolus regimens are particularly advantageous in settings that prioritize shorter hospital stays or outpatient management, offering a more convenient and cost-effective approach. These regimens also provide the flexibility of repeat treatments if necessary, enhancing patient care adaptability. Extensive clinical studies have validated Atosiban's efficacy and safety across its various dosing regimens. Although Atosiban has a high initial cost compared to its alternatives, such as β2-agonists and calcium channel blockers, its superior safety profile and targeted action result in fewer maternal and fetal side effects, thereby reducing overall healthcare costs. The ability to manage sPTL with shorter regimens alleviates the strain on healthcare resources and minimizes the need for intensive neonatal care, with significant cost savings. Overall, Atosiban represents a valuable therapeutic option for managing preterm labour. Its proven efficacy, safety, and cost-effectiveness make it a preferred choice for tocolysis, particularly in high-risk pregnancies like those with diabetes or cardiac issues.

Keywords: Preterm labour, Atosiban, Tocolysis, Oxytocin-receptor antagonist, Preterm birth

INTRODUCTION

Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation, is the primary cause of neonatal mortality and is associated with long-term health consequences. Preterm newborns face higher risks of adverse outcomes compared to full term babies, with the risk increasing with earlier gestational ages. This poses a significant global health burden, leading to various short-term and long-term complications, such as impaired growth and cognitive development, as well as early onset of chronic illnesses.[1]

Epidemiology

According to a 2020 study in The Lancet journal, India had a preterm birth rate of 13%, contributing to 20% of all preterm births worldwide, totalling 3.02 million, the highest globally. The high incidence in India is partly due to its large population, high birth rate, and challenges in providing high-quality antenatal care.[1]The prevalence of PTB is high and varies between different populations in India. Preterm delivery is significantly associated with various risk factors. The prevalence of PTB varies across different populations in India and is associated with risk factors such as pregnancy-induced hypertension, gestational diabetes, prior history of PTB, and maternal anaemia. Perinatal-neonatal period carries the highest risk of mortality and morbidity in the entire lifespan of a human being.[2]

Pathophysiology

The pathophysiology of PTB is complex, involving multiple pathological processes include activation of the

fetal hypothalamic-pituitary-adrenal axis, infections leading to inflammation, decidual haemorrhage or thrombosis, uterine distension, premature placental aging with oxidative stress, psychosocial stress, and genetic variations at multiple loci. Each of these factors contributes to the complex cascade of events that can precipitate preterm birth.[3]

Prevention of pre-term births

Prevention strategies for PTB include proactive or reactive measures. Proactive measures include assessing cervical length, administering prophylactic antibiotics, cerclage and using vaginal progesterone. Reactive interventions, such as tocolytics, are employed when proactive measures fail, aiming to delay preterm labour to allow for fetal maturation and improve neonatal outcomes.[4]

Justification for tocolysis

Tocolysis refers to the use of medications with the purpose of delaying the delivery of a foetus in women presenting preterm contractions. The primary objective of delaying preterm birth is to sustain gestation until fetal maturity is attained (i.e., beyond 36 weeks). However, an accepted goal is to prolong pregnancy, aiming for a minimum extension of 48 hours, providing a window of time to support treatments that have been shown to improve outcomes for delivery.[5] The use of tocolytics to delay delivery offers three key advantages: 1) provide enough time for full course of ante partum glucocorticoids to induce lung maturation 2) enabling in utero transfer to specialized tertiary care centers equipped with neonatal intensive care units (NICU) facilities 3) delayed delivery promotes fetal growth, maturation, and consequently, reduce perinatal mortality and morbidity.[6]

Current tocolytics options

Currently available tocolytic agents differ in their mechanisms of action, robust evidence base, efficacy, safety profile, cost, and licensing status. Atosiban and Ritodrine are the only tocolytics approved in India, with atosiban being specifically developed to treat sPTL. While alternatives such as calcium channel blockers (primarily nifidipine), β2-agonists (like isoxsuprine) and magnesium sulfate were developed and introduced for other medical indications, they were coincidently found to have tocolytic properties and are now being used off-label for that purpose.[4] Table 1 summarizes various tocolytic drugs used.

ATOSIBAN

Atosiban is extensively utilized on a global scale. The Central Drugs Standards Control Organization (CDSCO) in India granted approval for atosiban on 16 September 2015 for its use in preventing preterm labour. Atosiban received global approval in 2000 and is currently utilized as a primary tocolytic medication in over 68 countries, including the UK, Germany, China, France, Spain, Italy, Sweden, and Denmark. Following its approval in India in 2015, atosiban has undergone extensive research.

Mechanism of action

Atosiban, a synthetic peptide acts as a competitive vasopressin/oxytocin receptor antagonist (VOTra). Oxytocin (OT) and arginine vasopressin (AVP) potently induce myometrial contractions by stimulating OT receptors and V1a receptors in the uterus. Atosiban binds to oxytocin receptors, decreasing both the frequency and intensity of uterine contractions, thereby suppressing uterine contractile activity and inducing uterine quiescence.

Furthermore, it acts as a vasopressin receptor antagonist and may impact prostaglandin F (PGF2α) signaling pathways, which normally contribute to the onset and maintenance of labour. Atosiban has also been shown to preferentially relax uterine arteries, improving endometrial or uterine perfusion. Uterine relaxation occurs swiftly after atosiban administration, with a notable decrease in contractions within 10 minutes, achieving a stable state of uterine quiescence (≤4 contractions/hour) lasting for 12 hours. Both oxytocin and vasopressin play roles in the induction and maintenance of uterine contractions during labour.[10,11] Figure 1 shows peptide structure similar to oxytocin (only Difference at Positions- 1,2,4,8).

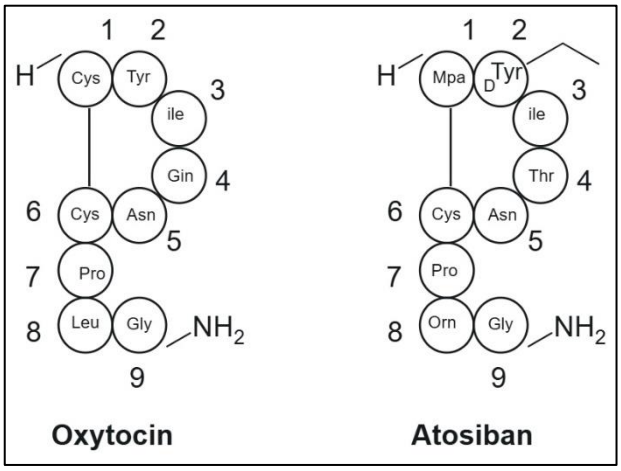

Figure 1: Atosiban=Peptide structure similar to oxytocin (only difference at positions-1,2,4,8).

Pharmacokinetics

Atosiban reaches steady-state plasma concentrations within one hour of infusion (300 mcg/min for 6 to 12 hours) and has a rapid decline in plasma concentration after infusion with an initial (tα) and terminal (tβ) half-life of ~12 min and ~ 1.7 hours, respectively. Atosiban passes the placenta. Following an infusion of 300 micrograms/min in healthy pregnant women at term, the fetal/maternal atosiban concentration ratio was 0.12. Atosiban is found in only small quantities in urine, its

urinary concentration is about 50 times lower than that of metabolite 1 (M1).[10]

Dosage and administration.[10]

The recommended protocol is as follows.

Atosiban

0.9 ml intravenous bolus 6.75 mg injection given over 1 minute, 3 hours intravenous loading infusion at a rate of 24 ml/hour (300 µg/min) 54 mg. Up to 45 hours' subsequent intravenous infusion at the rate of 8 ml/hour (100 µg/min) up to 270 mg. The total dose given during a full course of atosiban therapy should preferably not exceed 330.75 mg of atosiban.

Patients with renal or liver impairment

There is no experience with atosiban treatment in patients with impaired liver or kidney function. Renal impairment is not likely to warrant a dose adjustment, since only a small extent of atosiban is excreted in the urine. In patients with impaired hepatic function, atosiban should be used with caution. Atosiban is unlikely to inhibit hepatic cytochrome P450 isoforms in humans.[10] 48-hours administration of Atosiban does not seriously alter uterine and fetal arterial blood flow patterns.[12] Table 2 provides the indications and contraindications for atosiban.

ATOSIBAN: CLINICAL EVIDENCE

Phase I and Phase II

Atosiban, initially documented in the literature as an oxytocin receptor antagonist in 1985, was later tailored into a tocolytic agent by 1994.[13]

Phase II trials of Atosiban assessed its efficacy and optimal dosage for treating preterm labour. One study with 62 women showed 61% achieved uterine contraction cessation, and 70% achieved successful tocolysis. Another study with 302 women compared Atosiban with ritodrine, concluding Atosiban's effectiveness as a tocolytic agent against placebo and ritodrine, warranting further evaluation in larger trials.[14,15]

Phase III studies

Phase III trials provided robust evidence of Atosiban's efficacy and safety in a larger population of pregnant women experiencing preterm labour.

A trial conducted by Dewan et al. in 2016 involved 110 pregnant women between 24 to 34 weeks' gestation who exhibited signs of preterm labour. Atosiban was administered, and patients were monitored at 24,48 and 72hours post-treatment. The study found that 89.09% of the women remained undelivered after 72 hours, and 88.18% until discharge. Atosiabn effectively delayed labour in all twin as well as quadruplet pregnancies, with no maternal or fetal adverse events.[16]

In another study conducted over a year by Shaikh et al. in 2016 evaluated the impact of Atosiban on uterine activity using a tocodynamometer in 60 women. Atosiban delayed labour by more than 48hours in 86.7%, patient with a quadruplet pregnancy delivered after 72 hours on day 4, significantly reducing the uterine activity with minimal side effects, such as nausea (10%) and headache (1%), establishing a preferred tocolytic for managing preterm labour.[17]

Phase IV studies

Several Phase IV studies have been published in recent years demonstrating the use of atosiban in clinical practice with full-course (48 hours), brief-course (14 hours), and bolus dose regimens.

Bolus dose regimen

Dewan et al in September 2023 study was assessed a single bolus dose of atosiban's effectiveness and safety in delaying premature delivery for potential outpatient preterm labour management. They enrolled 75 symptomatic patients and administered a solitary atosiban bolus dose, which successfully delayed delivery in 68% of patients for an average of 13.3 days. No adverse effects were reported, highlighting the regimen's potential for short-term relief in outpatient settings.[18]

Brief course regimen (14 hrs)

A brief 14-hour regimen of Atosiban was tested by Dewan et al in April 2023 in a prospective study involving 50 women This regimen included a 14-hour treatment with a Brief dose (6.75 mg), followed by an infusion of 300 mcg/min for 2 hours and 100 mcg/min for the next 12 hours, using 3 vials of 5 ml each. Results showed 70% remained undelivered after 48 hours, and 58% after 7 days, with a mean delivery delay of 18.13 days. No adverse events were reported for mothers or foetuses. This regimen proved safe and effective, offering convenience, reduced hospital stays, and lower treatment costs. Larger clinical trials are needed to confirm these findings.[19]

Full course regimen (48 hrs)

A prospective observational study conducted by Bhatt et al. in 2021 at a North Indian tertiary care hospital administered intravenous Atosiban to 150 pregnant women (singleton or twin) for 48 hours. The treatment successfully delayed preterm deliveries by at least 48 hours in 97.3% of cases, with 140 pregnancies remaining undelivered for over 7 days, some up to 5 weeks. No adverse effects were reported in mothers and fetuses, except for one neonatal death due to sepsis. [20]

Gupta et al, conducted a one-year prospective, open-label, non-comparative study involving 72 pregnant women. Atosiban was administered intravenously over 48 hours in three stages. Patient evaluation occurred at 24-, 48-, and 72-hours post-treatment, with a final assessment at discharge by the 7th day. Results showed Atosiban delayed preterm labour for ≥48 hours in 23.50% of cases, ≥72 hours in 70.50% of cases, with 5.80% remaining undelivered for ≥7 days without requiring an alternative tocolytic agent or retreatment.[21]

Table 1: Overview of various tocolytic agents used for the treatment of PTL available in India.[7-9]

Tocolytic agent`	CDSCO approved	Contraindications	Maternal side effects	Fetal and neonatal side effect
Beta-mimetics Isoxsuprine, Ritodrine	Yes- Ritodrine No- Isoxsuprine	Cardiac arrhythmias, poorly controlled thyroid disease and diabetes mellitus	Tachycardia, hypotension, tremors, palpitations, pulmonary edema, hypokalemia, hyperglycemia	Tachycardia, fetal hyperglycemia, neonatal hypoglycemia & hypocalcemia, hypotension and myocardial ischemia
Calcium channel blockers Nifedipine	No	Cardiac disease, caution in renal impairment, maternal hypotension and with MgSO4	Headache, flushing, nausea, dizziness, transient hypotension and tachycardia	Sudden fetal death & distress
Oxytocin receptor antagonists Atosiban	Yes	None	Nausea (short duration), vomiting, chest pain (rarely), allergic reaction, headache	None noted as yet
PG synthetase inhibitors Indomethacin, ketorolac	No	Significant renal or hepatic impairment, active peptic ulcer disease, coagulation disorders, thrombocytopenia	Heartburn, nausea, gastritis, impairment of renal function, increased PPH, dizziness	Constriction of ductus arteriosus, pulmonary hypertension, oligohydramnios-intraventricular hemorrhage, necrotizing enterocolitis
NO donors GTN (glyceryl-trinitrate)	No	Headache	Headache, hypertension	Neonatal hypotension

Table 2: Provides the indications and contraindications for atosiban.

Indication[7]
Atosiban is indicated to delay imminent pre-term birth in pregnant adult women with: regular uterine contractions of at least 30seconds duration at a rate of ≥4 per 30 minutes A cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of ≥50% A gestational age from 24 until 33 completed weeks A normal fetal heart rate
Relative contraindication [7]
Atosiban must not be used in the following conditions: Gestational age below 24 or over 33 completed weeks Premature rupture of the membranes >30 weeks of gestation Suspected intrauterine infection Antepartum uterine haemorrhage requiring immediate delivery Intrauterine foetal death Eclampsia and severe pre-eclampsia requiring delivery Fetal distress Placenta praevia Abruptio placenta Any other conditions of the mother or fetus, in which continuation of pregnancy is hazardous Hypersensitivity to the active substance

Table 3: Summary of major clinical trials conducted on atosiban.

S. no.	Authors, years	Study design	Sample size	Results	Remarks
1.	Dewan et al[23], 2024	Prospective multicentric study Intervention: Atosiban over 48 hours in three successive stages	N=406	89% experienced a prolonged gestation period of > 48 hours with 83.75% continuing their pregnancy for up to 72 hours. For singleton pregnancies, the rate of prolongation for 72 hours was 84.95%, and twin pregnancies was 67.86%. Average gestational period extended by 31.28 days	Nausea (2.71%), tachycardia (2.46%), headache (1.97%)
2.	Singh et al[22], 2024	RCT Intervention Group 1 Atosiban over 48 hours in three successive stages Group 2- capsules of Nifedipine 20 mg up to a maximum dose of 40 mg during the first hour	Total N=150 Group I- Atosiban group (n=60) Group 2- Nifedipine group (n=70)	Group 1 = overall 95% (n=60) undelivered women at the end of 48 hours, 96.49% remain free from contraction for the first 24 hours. Group 2- About 54% of women (n=70) needed early drug termination	Group 1; mild gastrointestinal upset (28%, n=60). Group 2: hypotension (21.42%, n=70)
3.	Dewan et al[19], 2023	Open label, non-comparative study Intervention: Atosiban Brief course for 14 hrs	N=50	70% remained undelivered after 48 hours. 58% remained undelivered after 7 days. Mean delay in delivery: 18.13 days	No adverse events reported
4.	Dewan et al[18], 2023	Prospective study Intervention: An intravenous single bolus dose (6.75 mg/0.9 ml) of Atosiban was administered over a span of one minute.	N=75	Successfully delayed delivery in 68% of the patients for an average of 13.3 days	No adverse events reported
5.	Gupta et al[21], 2023	Open label, non-comparative study Intervention: Atosiban over 48 hours in three successive stages	N=72	Atosiban was successful in delaying preterm labour for: ≥ 48 hours in 23.50%, ≥ 72 hours in 70.50%, 5.80% women remained undelivered for ≥7 days	No adverse events reported
6.	Bhatt et al. 2021[20]	Prospective Cohort Study Intervention: Atosiban over 48 hours in three successive stages	N=150	Atosiban successfully delayed the preterm deliveries by ≥ 48 hours in 146 (97.3 %) pregnant women, 140 pregnancies remained undelivered for >7 days and some of them even up to 5 weeks.	No adverse events reported

Continued.

S. no.	Authors, years	Study design	Sample size	Results	Remarks
7.	Ganla et al[24] 2021	Case Report Intervention: 48- hour intravenous atosiban infusion (full course) on 4 different occasions at 28, 28.5, 30.4 and 31.4 weeks of gestation	A female patient with twin pregnancy	The gestation of women who reported preterm labour at 28th week, was extended to 34th week by repeated use of Atosiban treatment cycles.	No safety concerns for either mother or fetus in twin pregnancy
8.	Khalil et al[25] 2019	Retrospective observational study Intervention: Atosiban over 48 hours in three successive stages	N=84 Two groups were made according to cervical dilation (<2 and >2cm)	Mean gestational age at delivery was 35 weeks (SD 1,3) and 33,2 weeks (SD 1,1) for cervical dilation. 22,5% and 46% of both groups respectively delivered within 7 days of the diagnosis	No reported complications
9.	Baev et al[26] 2018	RCT Intervention: Group 1- Atosiban over 48 hours in three successive stages Group 2- 20 mg orally initially, then another 20 mg after 30 minutes if contractions persist, followed by 20 mg every 3–8 hours for up to 48 hours as needed	N=111 Nifedipine (n=54) Atosiban (n=57)	Nifedipine: 14.8% failure rate and more side effects, Atosiban: more effective in prolonging pregnancy. After excluding non-compliant patients, both drugs were equally effective for 48-hour prolongation, but atosiban extended pregnancy duration significantly longer than nifedipine.	Women receiving nifedipine were more likely to have hot flushes, palpitations, dizziness and hypotension
10.	Dewan et al[16], 2016	A, open label, non-comparative study Intervention: Atosiban over 48 hours in three successive stages	N=110	Patients (89.09%) remained undelivered up to 72 hrs after completion of treatment phase, 97 patients (88.18%) till the end of their hospital stay (upto 7 days)	No adverse events reported
11.	Shaikh et al[27], 2016	Open label, non-comparative study Intervention: Atosiban over 48 hours in three successive stages	N=60	Delayed the preterm labour by 48 hours and beyond in 86.7% of the patients.	No serious maternal or fetal adverse events were observed during the entire course of treatment and follow-up
12.	Xu et al[27], 2016	RCT Intervention: Atosiban Short Course (18hrs) Atosiban Long course (45hrs)	N=60 twin pregnancy Short course =30 Long course =30	48-hour effective tocolysis: Long course: 96.7% (29/30) Short course: 73.3% (22/30) 7-day effective tocolysis: Long course: 80.0% (24/30) Short course: 46.7% (14/30)	The incidence was reported to be 6.7% for both treatment group

Continued.

S. no.	Authors, years	Study design	Sample size	Results	Remarks
13.	Vliet et al[28] 2016 Apostel III	RCT Intervention: Nifedipine: Initial: 20 mg orally (two 10 mg capsules) in the first hour, followed by 20 mg slow-release nifedipine every 6 hours for 47 hours. Atosiban over 48 hours in three successive stages	N=510 Nifedipine =254 Atosiabn = 256	48 h of tocolysis with nifedipine or atosiban results in similar perinatal outcomes	Atosiban has favorable maternal adverse effects compared to nifedipine
14.	Saleh et al[29], 2013	Retrospective study Intervention: Atosiban over 48 hours in three successive stages Nifedipine: Initial 20 mg orally, then adjust to 10–20 mg 3–4 times daily based on uterine activity for up to 48 hours.	N=75 Atosiban group = 34 Nifedipin group =41	68.3% of women in the atosiban group remained undelivered at 7 days or more. 64.7% in the nifedipine group	Flushing, palpitation and hypotension were significantly higher in the nifedipine group
15.	Kashanian et al[30], 2005	RCT Intervention: Nifedipine: Initial dose: 10 mg sublingually every 20 min for 4 doses. If contractions inhibited, continue orally: 20 mg every 6h for 24h, then 20 mg every 8h for 24h, and finally 10 mg every 8h for 24h Atosiban maximum of 12 hours or until 6 hours after the patient's contractions ceased	N=80 Atosiban group = 40 Nifedipin group =40	Atosiban effective in 82.5% of cases, and Nifidipine in 75% of the cases (p = 1.000), for delaying delivery for 48 h Atosiban was effective in 75% of the cases, and Nifidipine in 65% of the cases, for delaying delivery for more than 7 days	The maternal side effects in the atosiban group were 17.5%, and in the Nifidipine group they were 40%, which had a statistically significant difference (p = 0.027)
16.	The French/ Australian investigators group[31], 2001	Multicentre, double blind- double, double-placebo, RCT Intervention: Atosiban (48 h) and salbutamol (2.5–45 µg/min) 48 h	N=241 Atosiban (n=119) or salbutamol (N=122).	Tocolytic effectiveness at 48 h was 93.3 versus 95.0% (P=0.67) and after 7 days was 89.9 versus 90.1% (P=0.93) in the atosiban and salbutamol groups, respectively, Tocolytic efficacy and tolerability within 48 h was 79.8 versus 75.2% (P=0.15), and after 7 days was 58.8	Maternal adverse events, including serious events, occurred more frequently in the salbutamol group. Neonatal outcomes comparable between the study groups

Continued.

S. no.	Authors, years	Study design	Sample size	Results	Remarks
				versus 46.3% (P=0.021) in the atosiban and salbutamol groups, respectively.	
17.	The European atosiban study group[32], 2001	Three multinational, multicentre, double-blind, RCT Intervention: Atosiban for 48hrs Or beta-agonist (ritodrine, salbutamol or terbutaline iv; dose titrated) for at least 18h and up to 48 hours	N=733 Atosiban group=363 Beta-agonist (n = 379; ritodrine, salbutamol or terbutaline)	No significant differences between atosiban and b-agonists in delaying delivery for 48h (88.1% vs 88.9%) or seven days (79.7% versus 77.6%)	Maternal side effects, particularly cardiovascular adverse events (8.3% vs 81.2%, P, 0.001), were reported more frequently in women given b-agonists, more treatment discontinuations due to side effects
18.	Moutquin et al[33], 2000	Multicenter, double-blind, RCT Intervention: Atosiban infusion for 48hrs Or ritodrine for 18 hours	N=252 Atosiban= 128 Ritodrine= 124	The proportion of women who had not been delivered at 48 hours was 84.9% (n=107) in the atosiban group and 86.8% (n=105) in the ritodrine group. Intravenous therapy was terminated more frequently as a result of maternal adverse events in the ritodrine group (29.8%) than in the atosiban group (0.8%)	The incidence of maternal cardiovascular side effects was lower in the atosiban group (4.0% vs 84.3%, P < .001)
19.	Romero et al[34], 1997	Multicenter, double-blind, placebo-controlled trial Intervention: Atosiban infusion for 48hrs	N=501 Atosiban group= 246 Placebo group= 255	The percentages of patients remaining undelivered and not requiring an alternate tocolytic at 24 hours, 48 hours, and 7 days were significantly higher in the atosiban group than in the control group (all P ≤ .008)	Injection-site reactions observed with atosiban
20.	Goodwin et al[14], 1994	RCT Intervention: Atosiban (300 µg/min) or bolus for 2 hours	N=120 Atosiban group= 60 Placebo group = 60	The mean percent decrease in contraction frequency was greater in atosiban subjects compared with controls (55.3% ± 36.3% vs 26.7% ± 40.4%, mean ± SD)	Nausea and vomiting in 1 atosiban patient

Table 4: Atosiban vs other tocolytics.

S. no.	Apart from the atosiban, none of the tocolytics are uterospecific.[7]
1.	Atosiban have superior efficacy without the conventional cardiovascular side effects.[7]
2.	Can be used in cardiac patients such as those with rheumatic heart disease[8]
3.	Well-controlled insulin-dependent diabetic women with SPTL can safely be treated with atosiban[9]
4.	Can be used in twins and higher-order multiple births where beta-agonists and CCB are contraindicated[9]

Table 5: Atosiban regimens for preterm labour management.

Regimen	When to use	Advantages	Pharmacoeconomics	Dosage and administration
Bolus dose	For short-term management of preterm labour. Suitable for outpatient settings. For patients who may not require prolonged tocolysis.	Quick onset of action. Minimal side effects. Convenient for outpatient management.	Reduces costs associated with extended hospital stays. Provides a cost-effective option for short-term tocolysis.	Single bolus dose: 6.75 mg over 1 minute.
Brief course	When a shorter hospital stay is desired. For patients who may benefit from a shorter duration of treatment	Shortens hospital stay. Reduces healthcare costs. Flexible and convenient for both patients and hospital staff.	Significantly lowers the cost of treatment by reducing the duration of hospitalization. Allows for potential repeat treatments.	Bolus dose: 6.75 mg over 1 minute. Infusion: 300 µg/min for 2 hours. Maintenance infusion: 100 µg/min for 12 hours. Total duration: 14 hours. Uses 3 vials of 5 ml each.
Full course	For managing imminent preterm birth when prolonged tocolysis is needed. Suitable for high-risk pregnancies (e.g., diabetes, cardiac conditions)	Provides the longest duration of labour delay (up to 48 hours). Allows for comprehensive maternal and fetal monitoring.	Reduces overall healthcare costs by decreasing the need for prolonged NICU stays. Minimizes maternal and fetal adverse effects.	Initial bolus: 6.75 mg over 1 minute. Loading infusion: 24 ml/hour (300 µg/min) for 3 hours. Maintenance infusion: 8 ml/hour (100 µg/min) for up to 45 hours. Total dose: 330.75 mg.

Table 6: OT/AVP antagonist therapeutics and ongoing clinical trials.

S. no.	Company	Drug	Design	Findings
1.	ObsEva	Nolasiban (OBE-001)	RCT	Terminated
2.	GSK	Retosiban	RCT	Terminated
3.	Ferring Pharma	Barusiban	RCT	No reduction in delivery within 48 h

A study conducted by Singh et al. at S.N. Medical College and Hospital, Agra, India, from September 2017 to August 2019, involved 150 women randomly assigned to the Atosiban and Nifedipine groups. Among women with a Bishop score >7, 6.67% required more than 132.75 mg of Atosiban, with 28% experiencing adverse effects, mainly mild gastrointestinal upset. In contrast, 54% of the Nifedipine group women required early termination due to adverse effects, primarily hypotension. At 48 hours, Atosiban infusion resulted in 95% of women remaining undelivered, with 96.49% free from contractions in the first 24 hours. Atosiban was better tolerated, demonstrating superior safety and maternal profile compared to Nifedipine. The study underscores the need for direct comparison of oxytocin antagonists and calcium channel blockers for their tocolytic efficacy and neonatal outcomes.[22]

A recent large scale study conducted by Dewan et al. in February 2024 involved 406 pregnant patients who exhibited symptoms of preterm labour. The results of the study revealed that 89% of the patients experienced a prolonged gestation period of more than 48 hours, with 83.75% of them continuing their pregnancy for up to 72 hours. For singleton pregnancies, the rate of prolongation for 72 hours was 84.95%, while for twin pregnancies, it

was 67.86%. On average, the gestational period was extended by 31.28 days, and the neonates had favorable outcomes. Only a small percentage of patients reported adverse events such as nausea, tachycardia, and headache, and no new or unexpected adverse events were observed. Therefore, Atosiban proved to be effective in prolonging the gestational period, with a low incidence of adverse effects. This could potentially reduce the need for Neonatal Intensive Care Unit admission and associated costs.[23]

Safety prolife

Atosiban, being utero-specific, exhibits feto-maternal and neonatal side effects comparable to placebo, with only nausea being statistically more common, primarily linked to bolus injection. Common minor side effects include nausea, headache, dizziness, and palpitations.[4,7]

Embryo-fetal toxicity studies have not shown toxic effects of atosiban. Atosiban can be safely used in expanded blood volume, anemia, where use of other tocolytics predispose to pulmonary edema. Atosiban crosses the placenta in an average fetal versus maternal ratio of 0.124. Drug concentrations in the fetal circulation do not increase with longer infusion rates, suggesting that the drug does not accumulate in the fetus.[12]

A follow-up study of infants born after tocolysis with atosiban revealed no ill effect on their psychosocial and motor development up to the age of two years.[35]

Atosiban vs β-mimetics

Atosiban has consistently demonstrated a superior safety profile compared to β-mimetics, such as isoxsuprine and ritodrine, in the management of preterm labour. Clinical studies have shown that β-mimetics can negatively impact lactogenesis by reducing mammary gland tissue and decreasing milk production, likely due to the activation of the sympathetic system, which inhibits milk production. These adverse effects on lactation have not been observed with Atosiban. Studies have confirmed that the administration of atosiban during pregnancy does not affect the type of lactation in term newborns at hospital discharge.[36]

A pivotal study comparing atosiban and ritodrine further highlighted this difference in safety profiles. While both drugs were effective in delaying preterm labour, ritodrine was associated with a higher incidence of maternal side effects, including severe cardiovascular and metabolic disturbances. In contrast, atosiban, with its targeted mechanism as an oxytocin receptor antagonist, resulted in significantly fewer adverse events, making it a safer alternative, particularly in situations where maternal and fetal safety is paramount.[32,33]

Atosiban vs Nifedipine

While nifedipine is commonly used off-label for tocolysis, it is not utero-specific and has a higher incidence of multi-organ side effects, such as hypotension, flushing and palpitations. Nifedipine can be administered orally, but rapid onset preparations compromise safety and slow-release preparations compromise efficacy. It is contraindicated in woman with cardiac disease and should be used with caution in those with diabetes or multiple pregnancy due to the risk of pulmonary oedema.[7]

Pharmacoeconomics

The choice of tocolytic agent depends mainly on the availability following regulatory approval in the country, the drug efficacy and effectiveness, the foetal and maternal safety profiles, and the costs of treatment.[37] Betamimetics are commonly used for tocolysis, but their non-specific mechanism of action often leads to numerous adverse events across multiple organ systems, primarily cardiovascular in nature.

Atosiban has demonstrated comparable effectiveness to betamimetics but with lower costs due to its superior safety profile. From the perspectives of payers, hospitals, and overall healthcare systems, atosiban offers cost savings compared to betamimetics in the treatment of preterm labour. These cost savings stem from atosiban's superior safety profile. Table 5 outlines various regimens of atosiban.

Other oxytocin/arginine - vasopressin - receptor antagonists

Barusiban, a selective peptide oxytocin antagonist, exhibits high affinity for the human oxytocin receptor (OTR) while demonstrating low affinity for the V1a receptor. It boasts increased potency and prolonged action compared to atosiban. In nonhuman primates, barusiban effectively inhibits oxytocin-induced myometrial contractions.[38] However, despite promising preclinical findings, barusiban did not demonstrate efficacy over placebo in phase II clinical trials regarding the reduction of uterine contractions or the proportion of patients delivering within 48 hours.

In addressing this challenge, researchers are exploring non-peptides like retosiban, which exhibit high selectivity for the oxytocin receptor. However, a systematic review evaluating three clinical trials testing retosiban for managing preterm birth did not reveal a significant benefit in extending pregnancies compared to placebo.[39] Atosiban is currently the only oxytocin receptor antagonist used clinically. Table 6 summarizes various OT/AVP antagonist.

CONCLUSION

The admission of premature newborns to NICUs, especially in private hospitals, imposes a significant financial burden on parents. This often forces them to make difficult decisions, such as declining treatment or seeking care in government-supported NICUs in low and middle-income countries where costs are lower or covered.

In cases of preterm or threatened preterm labour, tocolysis is administered to delay labour, allowing time for steroids to take effect or for transferring the mother to a suitable neonatal unit. Despite atosiban's proven safety and efficacy, its primary barrier has been cost. However, recent clinical evidence supports more cost-effective bolus and brief duration regimens. Pharmacoeconomic evaluations have shown significant cost savings with atosiban compared to β2-agonists and calcium channel blockers, mainly due to reduced side-effect management costs. Atosiban also results in fewer feto-maternal side effects, lower treatment discontinuation rates, and shorter hospital stays.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. The Lancet. 2023;402(10409):1261-71.
2. Bhakoo ON, Kumar P. Current challenges and future prospects of neonatal care in India. The Ind J Pediat. 2013;80:39-49.
3. Coler BS, Shynlova O, Boros-Rausch A, Lye S, McCartney S, Leimert KB, et al. Landscape of preterm birth therapeutics and a path forward. J Clin Med. 2021;10(13):2912.
4. Lamont RF, Jørgensen JS. Safety and efficacy of tocolytics for the treatment of spontaneous preterm labour. Current Pharmaceutical Design. 2019;25(5):577-92.
5. Wex J, Abou-Setta AM, Clerici G, Di Renzo GC. Atosiban versus betamimetics in the treatment of preterm labour in Italy: clinical and economic importance of side-effects. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2011;157(2):128-35.
6. Lamont RF, Kam KR. Atosiban as a tocolytic for the treatment of spontaneous preterm labour. Expert Rev of Obst Gynecol. 2008;3(2):163-74.
7. FOGSI Focus-Prevention of Pre-Term Labour – 2017 The Federation of Obstetric and Gynecological Societies of India. 2017. Available at: https://www.fogsi.org/wp-content/uploads/fogsi-focus/fogsi-focus-ptl.pdf. Accessed on 17th June, 2024
8. Coelho K, Gupta M. Role of isoxsuprine as a tocolytic agent in the management of preterm labor in Indian clinical practice. Int J Reprod Contracept Obstet Gynecol. 2024;13:483-91.
9. Di Renzo GC, Roura LC, European Association of Perinatal Medicine-Study Group on "Preterm Birth". Guidelines for the management of spontaneous preterm labour
10. Tractocile 7.5 mg/ml concentrate for solution for infusion. Available at: medicines.org.uk. Accessed on 12th July 2024.
11. Koshimizu TA, Nakamura K, Egashira N, Hiroyama M, Nonoguchi H, Tanoue A. Vasopressin V1a and V1b receptors: from molecules to physiological systems. Physiological reviews. 2012;92(4):1813-64.
12. Grzesiak M, Wilczynski J. Preliminary report of 48-hours Atosiban administration in spontaneous preterm labour - Doppler blood flow assessment of placental and fetal circulation. Neuro Endocrinol Lett. 2013;34(7):681-6.
13. Åkerlund M, Carlsson AM, Melin P, Trojnar J. The effect on the human uterus of two newly developed competitive inhibitors of oxytocin and vasopressin. Acta obstetricia et gynecologica Scandinavica. 1985;64(6):499-504
14. Goodwin TM, Paul R, Silver H, Spellacy W, Parsons M, Chez R, Hayashi R, Valenzuela G, Creasy GW, Merriman R. The effect of the oxytocin antagonist atosiban on preterm uterine activity in the human. American J Obst Gynecol. 1994;170(2):474-8.
15. Goodwin TM, Valenzuela G, Silver H, Hayashi R, Creasy GW, Lane R. Treatment of preterm labour with the oxytocin antagonist Atosiban. American J Perinatol. 1996;13(03):143-6.
16. Dewan B, Shah D. The clinical experience of atosiban in preterm labour. British J Med Res. 2016;13(7):1-9.
17. Shaikh S, Mayekar R, Bhosale A, Nandanwar Y, Dewan B. Atosiban–Its impact on uterine activity in preterm labour. British J Med Res. 2016;18(2):1-8.
18. Dewan B, Shinde S. Acute Tocolysis Using a Single Bolus Dose of Atosiban for Preterm Labour Management: A Prospective Study. J Gynecol Obst. 2023;11(5):120-4.
19. Dewan B, Shinde S. Clinical safety and efficacy of atosiban brief duration 14-hour treatment regimen in delaying preterm labour. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2023;12(6):1862-5
20. Bhatt A. Initial experience with the oxytocin antagonist atosiban for preterm labour in a tertiary care centre: prospective observational cohort study Eur J Biomed Pharma Sci. 2021;8(6):470-6.
21. Gupta N, Jahan U, Shukla S, Usmani F. Study to evaluate the efficacy and safety of Atosiban in preterm labour in North Indian population. Int J Clin Obst Gynaecol. 2023;7(3):371-5.
22. Singh P, Singh S, Singh D, Thakur A, Dhakar JS, Singh TP. Study on Safety and Efficacy of Atosiban and Nifedipine in the Management of Threatened

Preterm Labour. SSR Inst Int J Life Sci. 2024;10(2):5209-14.
23. Dewan B. Oxytocin antagonist Atosiban for the treatment of preterm labour: clinical trial evidence. London J Med Health Res. 2024;24(1):35-45.
24. Ganla KN, Vora PH, Choudhary RA, Ganla MK, Joshi P, Desai K. Multiple re-treatments with Atosiban, an oxytocin receptor antagonist helps to delay the preterm labour successfully. Acta Scientific Women's Health. 2021;3(5):2582-3205.
25. Khalil MA, Saad R, Ibrahim AA. Initial cervical dilation and the association of the success of atosiban. Int J Pregn & Chi Birth. 2019;5(2):103-6.
26. Baev OR, Vasil'chenko O, Karapetyan AO, Tetruashvili NK, Khodzhaeva ZS. A comparison of tocolysis with nifedipine or Atosiban in preterm. Akusherstvo i Ginekologiya. 2018;5:50-6.
27. Xu YJ, Ran LM, Luo XH, Zhai SS, Zhou ZY, Zhang YY, et al. Clinical efficacy of atosiban treatment in late abortion and preterm labour of twin pregnancy. Int J Clin Exp Med. 2016;9(2):3946-52.
28. Van Vliet EO, Nijman TA, Schuit E, Heida KY, Opmeer BC, Kok M, et al. Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. The Lancet. 2016;387(10033):2117-24.
29. Saleh SS, Al-Ramahi MQ, Al Kazaleh FA. Atosiban and nifedipine in the suppression of pre-term labour: a comparative study. J Obst Gynaecol. 2013;33(1):43-5.
30. Kashanian M, Akbarian AR, Soltanzadeh M. Atosiban and nifedipin for the treatment of preterm labour. Int J Gynaecol Obstet. 2005;91(1):10-14.
31. French/Australian Atosiban investigators group. Treatment of preterm labour with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. European J Obs Gynecol Reprod Bio. 2001;98(2):177-85.
32. versus Beta-agonists TW. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. Brit J Obst Gynaecol. 2001;108(2):133-42.
33. Moutquin JM, Sherman D, Cohen H. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labour: a multicenter effectiveness and safety study. Am J Obstet Gynecol. 2000;182(5):1191-9.
34. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labour: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. Am J Obst Gynecol. 2000;182(5):1173-83.
35. Schleußner E. The prevention, diagnosis and treatment of premature labour. Dtsch Arztebl Int. 2013;110(13):227-35.
36. López Gómez L. Oxytocin receptor antagonist (Atosiban) in the threat of preterm birth: does it have any effect on breastfeeding in the term newborn? Breastfeed Med. 2018;13(2):123-8.
37. Wex J, Connolly M, Rath W. Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation. BMC Pregnancy Childbirth. 2009;9:23.
38. Vrachnis N, Malamas FM, Sifakis S, Deligeoroglou E, Iliodromiti Z. The oxytocin-oxytocin receptor system and its antagonists as tocolytic agents. Int J Endocrinol. 2011;1:350546.
39. Pavlidis I, Stock SJ. Preterm birth therapies to target inflammation. J Clin Pharmacol. 2022;62:79-93.

Cite this article as: Dewan B, Navale S, Ganiga R. Atosiban: a comprehensive approach to preterm labour management. Int J Reprod Contracept Obstet Gynecol 2024;13:3420-31.