International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Mane S et al. Int J Reprod Contracept Obstet Gynecol. 2025 Jan;14(1):305-311
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20243975

Review Article

Role of isoxsuprine in acute and maintenance tocolysis

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Received: 12 November 2024
Accepted: 19 December 2024

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ABSTRACT

Preterm birth (PTB) continues to be a significant global health issue, with India reporting 3.02 million PTBs, accounting for nearly 23% of all PTBs worldwide. Over the past decade, the PTB rate has remained unchanged at 13 per 100 live births. Preterm labor (PTL), a leading cause of pregnancy-related hospitalizations, poses significant challenges for healthcare providers. Effective management is essential to mitigate the complications associated with PTB, which places a considerable burden on the healthcare system. Managing PTL is particularly challenging due to the difficulty in predicting its onset, as approximately 50% of PTB cases occur without identifiable risk factors. The current PTB detection methods, such as the transvaginal ultrasound (TVUS) examination, the fibronectin test, etc., fail to detect PTB accurately, which makes PTB a complicated condition. The primary goal of PTL management is to prolong pregnancy with tocolytics which provides an opportunity to administer antenatal corticosteroids and magnesium sulfate, if needed, as well as in utero transfer to higher care facilities, when necessary. This review delves into recommendation shared by expert gynecologists on the role of effective tocolysis in management of PTL. The experts shared insights that in India, isoxsuprine is preferred over other tocolytic agents in acute PTL management, allowing sufficient time for corticosteroids to act. However, they opined that there is a possibility of spontaneous recurrence of PTL after the cessation of active labour therapy, highlighting the importance of maintenance tocolysis. The use of oral isoxsuprine as maintenance tocolysis has been associated with improved perinatal outcomes, including lesser incidence of NICU admission, improved birth weight outcomes, and extended latency periods. Maintenance tocolysis can be given to patients of cervical cerclage, active and threatened PTL. In conclusion, while PTL remains a significant challenge, isoxsuprine use in both acute and maintenance phases of therapy can positively impact maternal and perinatal outcomes.

Keywords: Adverse birth outcomes, PTB, PTL, Corticosteroid therapy, Magnesium sulfate, Isoxsuprine, Calcium channel blockers, Beta-adrenergic receptor agonists, Oxytocin antagonist

INTRODUCTION

Preterm birth (PTB) remains a significant global health concern, being a leading cause of neonatal and under-five mortality. In 2010, India reported approximately 3.5 million PTBs, with a rate of 13.1 per 100 live births. By 2020, this rate saw little improvement, remaining at 13 per 100 live births. India reported 3.02 million PTBs, accounting for nearly 23% of the global total, making it the country with the highest number of preterm births and the fourth highest PTB rate in the world.[1] Newborns delivered preterm face significantly elevated risks of adverse health outcomes compared to those born at term. The likelihood of mortality and morbidity is directly correlated with the degree of prematurity. Extremely preterm infants (born at less than 28 weeks of gestation) are at the highest risk, followed by very preterm infants (28 weeks to less than 32 weeks), and moderate to late preterm infants (32 weeks to less than 37 weeks).[1] Preterm infants are particularly susceptible to a range of complications, including respiratory distress syndrome, chronic lung disease, intestinal injury, immune system compromise, cardiovascular disorders, hearing and vision impairments, and neurological damage.[2] A significant portion of neonatal care resources is directed toward these infants, who experience longer length of stay in neonatal intensive

care units (NICUs) and face a greater frequency of rehospitalizations compared to those born at term. This trend highlights the substantial healthcare burden associated with PTB.[3]

PTL is the primary reason for hospitalization during pregnancy. However, not all preterm contractions result in PTB, 50% of women hospitalized for PTL deliver at term. Identifying which women will deliver preterm is a key challenge for obstetricians.[4]

Inhibiting uterine contractions has been the focus of PTL treatment. It includes use of tocolytic drugs to inhibit contractions. Federation of obstetric and gynaecological societies of India (FOGSI) guidelines for the management of PTL recommend the utilization of tocolytics to prolong the gestational period, to enable the administration of corticosteroids and magnesium sulfate if needed.[4] International guidelines recommend the use of tocolytic drugs to delay delivery for a duration of 48 hours. However, it is common for tocolysis to be extended beyond this initial period (maintenance tocolysis) or to be reinitiated if a new episode of threatened PTL arises (repeated tocolysis).[5] Following successful treatment of an acute episode, women remain at risk for recurrent PTL, potential hospitalization, the need for retreatment with intravenous tocolytic agents, and PTB. In fact, almost 50% of women who receive treatment for acute PTL eventually experience preterm delivery.[6] Maintenance tocolysis is often prescribed to prolong pregnancy after an acute episode of PTL, with the aim of promoting uterine quiescence and reducing the risk of recurrent PTL. The effectiveness of maintenance tocolysis remains debated, with limited number of randomized controlled trials combined with methodological shortcomings, highlighting a significant gap in existing body of evidence. FOGSI guidelines recommend maintenance with isoxsuprine, which has superior fetal and maternal outcomes when administered in appropriate dosage.[7]

An advisory board meeting (ABM) was conducted in March 2024, with an expert panel of eight experts qualified in obstetrics and gynecology. At ABM, the experts discussed the role of tocolytic therapy in acute and maintenance phase for the management of PTL. The experts addressed various barriers/challenges with the use of tocolytic therapy. A literature search across databases such as PUBMED, COCHRANE, and Google Scholar was conducted for articles with keywords such as “PTL,” “preterm birth,” “tocolysis,” and “isoxsuprine,” “maintenance tocolysis.” The current guidelines for tocolysis were also critically reviewed, and a descriptive analysis of the literature and expert opinions are summarized below.

CHALLENGES ASSOCIATED TO PREDICT AND DIAGNOSE PTL

Early prediction of PTB is crucial in reducing miscarriage rates and preventing long-term complications in premature infants. However, half of the women who experience PTB do not present with known clinical risk factors, making prediction a significant challenge.[8] Cervical shortening is one of the earliest indicators of spontaneous preterm birth (sPTB), often detectable weeks before the onset of labor. However, individual PTB detection methods, such as TVUS or fetal fibronectin (fFN) testing, have limited accuracy, making early diagnosis of PTB a challenge.[9]

RISK FACTOR ASSESSMENT

A key risk factor for PTL is a previous history of PTB, with recurrence rates increasing to 14.3% after first episode of PTB and 28% after second episode. Other risk factors include multiple gestations, cigarette smoking, cervical incompetence, uterine anomalies, uterine overdistension (due to conditions like polyhydramnios or macrosomia), previous cervical surgery, early pregnancy bleeding, bacterial vaginosis, low socioeconomic or educational status, and extremes in maternal age. Despite advancements in screening and monitoring techniques, predicting PTL remains difficult, even among women considered to be at high risk.[7,8] Spontaneous PTL is a complex syndrome with multiple etiologies, including infection, uteroplacental disorders, cervical disease, and uterine overdistension. The clinical presentations, such as PTL or preterm premature rupture of membranes (PROM), vary depending on the underlying pathological processes and their timing, ultimately triggering the common parturition pathway. This causal heterogeneity complicates the development of universally effective prevention, diagnostic, and treatment protocols for preterm birth.[10]

CERVICAL LENGTH ASSESSMENT

Currently, mid-trimester cervical length (CL) assessment by TVUS is a recommended tool for the prediction of sPTB between 16-24 weeks of gestation for asymptomatic women with a history of PTB. The international society of ultrasound in obstetrics and gynecology (ISUOG) recommends universal screening through CL measurements between 18 and 24 weeks in singleton pregnancies, aiming to identify all women at risk of PTB. In contrast, the Royal college of obstetricians and gynaecologists (RCOG) advocates for targeted screening in women with specific risk factors such as prior PTB, cervical surgery, or congenital uterine anomalies, allowing for tailored interventions. Studies suggest that targeted screening may be more effective in identifying candidates for interventions like transvaginal cerclage, especially when CL is <25 mm.[10] In addition to universal or targeted screening approaches, single screening for PTB involves a one-time assessment of risk factors or CL. While this method can identify some women at risk, it may miss those who develop risk factors later in pregnancy, as a single measurement may not be sufficient for accurate prediction of spontaneous PTB in all cases. Serial screening, on the other hand, involves multiple assessments, such as transvaginal CL measurements from 16 to 24 weeks, and is particularly recommended for women with a history of

sPTB. This method allows for closer monitoring and timely interventions if cervical shortening is detected and has been shown to be more effective in identifying women at risk by accounting for changes in CL overtime.

fFN ASSESSMENT

In addition to CL, the fFN test is valuable in predicting PTB. TVUS often uses a CL cut-off of ≤25 mm, though women with a CL between 25-30 mm still face a risk of delivery within seven days. Enhancing predictive accuracy may be possible by combining CL measurement with quantitative fFN testing.[8] A negative fFN result indicates a low risk of PTB, while levels exceeding 200 ng/mL may warrant interventions such as in-utero transfer and the administration of antenatal corticosteroids. The fFN test is also useful for counselling patients and ensuring compliance with recommended care plans. Despite these screening tools, accurately identifying women at high risk for PTL remains a challenge.[10,12] The evidence supporting the use of fFN in predicting PTB is often of low quality, leading to uncertainty regarding its effectiveness, particularly in pregnancies less than 34 weeks' gestation. Various factors can interfere with the accuracy of fFN testing. Contamination of the test swab with lubricants, soaps, or creams can disrupt the absorption of cervicovaginal secretions, potentially altering assay results. False-positive results are another concern, particularly in the presence of vaginal bleeding or ruptured membranes, as fFN is normally found in maternal serum and amniotic fluid. Although fFN has clinical utility, challenges remain in enhancing its positive predictive value.[8,12]

EXPERTS' CONSENSUS

Incidence of PTB varies, with 5-13% of pregnancies affected. Contributing factors include assisted reproductive technology (ART), hypertension, advanced maternal age, cervical incompetence, previous PTL history, and low socioeconomic status. Regular CL monitoring is essential, with lengths under 2.5 cm indicating a higher risk of PTL. fFN testing is helpful for prediction; a negative result suggests a low likelihood of labor. Common presentation of PTL occurs between 28 and 32 weeks of gestation.

MANAGEMENT OF PTL

Given that uterine contractions are the primary precursor to preterm birth, therapeutic strategies have predominantly aimed at their cessation. This intervention, referred to as tocolysis, involves the suppression of myometrial contractions.[12] Upon diagnosing PTL, it is recommended to initiate treatment with tocolytic medications to extend the pregnancy by up to 48 hours. This delay provides opportunity for the administration of antenatal corticosteroids and magnesium sulfate, if indicated, and facilitates in utero transfer to higher-level care facilities when necessary.[13]

An essential objective is to postpone delivery sufficiently to enable the administration of corticosteroids, which can decrease the risks of neonatal respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, and overall perinatal mortality.[14] The American college of obstetricians and gynecologists (ACOG) also recommends corticosteroid administration as a primary strategy to improve neonatal outcomes in women at high risk of PTL.[14] Betamethasone and dexamethasone are the most frequently prescribed corticosteroids between 24 and 34 weeks of gestation to delay labor and promote fetal lung maturation.[15]

The efficacy of magnesium sulfate in fetal neuroprotection is well-documented. A Cochrane review indicated that antenatal magnesium sulfate administration to women at risk of PTL significantly lowers the risk of cerebral palsy and the incidence of severe gross motor dysfunction in their children.[14] Prophylactic antibiotic therapy is not recommended as a routine for women in PTL with intact membranes and no signs of infection.[16]

TOCOLYTICS FOR PTL, INDICATIONS, CRITERIA AND DURATION

Tocolysis, derived from the Greek words "tokos" (childbirth) and "lytic" (capable of dissolving), refers to the use of pharmacological agents to suppress uterine contractions. Tocolytics were first recognized in 1959.[17] In 1961, the beta-agonist, Isoxuprine was described as a first line tocolytic.

GOALS OF TOCOLYSIS IN ACUTE PTL

The primary objective of tocolysis is to prolong the pregnancy or, at a minimum, by 48 hours. This short extension allows for the administration of a single course of betamethasone (two 12 mg intramuscular doses, 24 hours apart), which can reduce perinatal mortality and morbidity by up to 50%. Another key aim of tocolysis is enabling in-utero transfer of the fetus to a specialized perinatal center, significantly reducing perinatal complications. However, in cases where the intrauterine environment is compromised, such as in infections, prolonging the pregnancy could result in fetal harm.[18]

Below are the criteria to initiate tocolysis[19]

Preterm spontaneous labor (CTG>4 uterine contractions in 20 min, or 6 in 60 min) and one of the following: Shortening of the cervix to ≤ 25 mm or by >5 mm over 2 hours (measured by transvaginal sonography), positive fibronectin test (optional), symptomatic placenta previa/low lying placenta with vaginal bleeding and cervical dilation of >2 cm and <5 cm.

Preterm spontaneous rupture of membranes before 34 weeks of gestation without signs of chorioamnionitis (optional, no general recommendation).

A variety of agents are used for the inhibition of acute PTL which differ from each other with respect to the mechanism of action, dose, route of administration, safety, and side-effects for mother and baby. Although variety of tocolytic agents are available for clinical use, there is no single, completely effective or side effect free tocolytic.[18]

BETAMIMETICS

Among the tocolytic agents, isoxsuprine, a betamimetic, is one of the most widely used tocolytic agents in India, administered intravenously or intramuscularly, with maintenance oral doses to manage PTL. Isoxsuprine is included as a treatment option in the FOGSI guidelines, and it is a preferred option among clinicians due to its effectiveness in prolonging pregnancy and improving perinatal outcomes.[7]

CALCIUM CHANNEL ANTAGONIST

Nifedipine, a calcium channel blocker, is used for PTL management with an oral dosage of 10-20 mg every 3-6 hours, though its side effects include hypotension, headache, flushing, and nausea. The concomitant administration of nifedipine and magnesium sulfate was not recommended as this can lead to neuromuscular blockade and fatal respiratory arrest, due to action of both molecules on blockage of calcium channels. Moreover, the use of nifedipine for PTL is not approved by the central drugs standard control organization (CDSCO) in India. The innovator has confirmed in an expert opinion published in 2014 that nifedipine has not been licensed for use in PTL or in pregnancy.[7]

OXYTOCIN RECEPTOR ANTAGONIST

Atosiban, an oxytocin receptor antagonist, is administered intravenously in three stages over 48 hours and is generally well-tolerated, with nausea and vomiting as the primary side effects. Experts from India opined that atosiban can be used in cardiac patients such as those with rheumatic heart diseases.[7]

NSAID DRUGS

Indomethacin, an NSAID, reduces prostaglandin synthesis and is given in a loading dose of 50 mg followed by 25 mg every 6 hours for 48 hours, though it carries risks such as gastrointestinal issues and renal complications.[7] NSAIDs should be used before 32 weeks of gestation to avoid the risk of patent ductus arteriosus closure if administered later.[19]

ISOXSUPRINE

Isoxsuprine, a beta-adrenergic agonist is a widely used tocolytic in India.[20,21] Several large clinical trials have demonstrated the therapeutic efficacy of isoxsuprine in patients at risk for PTL and miscarriage. These studies also highlight its favorable tolerability profile, both in threatened/active PTL when administered intravenously and during maintenance therapy through oral or intramuscular administration.[22] It is a CDSCO-approved medication used in India for over 60 years, induces relaxation of vascular smooth muscles and uterine smooth muscle, facilitating peripheral vasodilation and uterine relaxation.[7] The primary pharmacodynamic effects of isoxsuprine are mediated through three mechanisms: stimulation of β-adrenergic receptors, predominantly in the myometrium, leading to inhibitory relaxation of smooth muscle fibers; inhibition of α-adrenergic receptors in certain arteries; and direct spasmolytic action on smooth muscles and the myometrium, similar to the effects of papaverine.[23]

It is commonly prescribed for dysmenorrhea and PTL. Based on its effectiveness and safety, FOGSI has established a treatment protocol for isoxsuprine. It is a widely used tocolytic agent, with previous studies showing successful tocolysis in 100% patients for 48 hours, with 94% achieving vaginal deliveries. Systematic reviews indicate an efficacy rate of about 89% for isoxsuprine in managing PTL, whether administered intravenously or as maintenance therapy via intramuscular or oral routes.[21] The revised FOGSI regimen involves an initial IV infusion of 40 mg isoxsuprine diluted in 500 mL 5% dextrose, administered at a rate of eight drops per minute (0.04 mg/min). The rate should be increased by eight drops every 15 minutes until uterine quiescence is achieved, with infusion continued for 12 hours. Following uterine quiescence, intramuscular injections of 10 mg every 4 hours for 24 hours are given, and maintenance therapy consists of 40 mg sustained-release capsules twice daily and can be continued as per patient's response. Isoxsuprine is associated with minimal dose-dependent adverse effects such as nausea, constipation, tachycardia, palpitations, and hypotension, which can be managed through dose titration. The expert's consensus in Coelho et al shared that after increasing the drip rate, they wait for another 15 minutes to monitor pulse rate and blood pressure and then further increase the drip rate. This gradual dose titration helps prevent any potential side effects.[7,17]

Jaju et al retrospectively evaluated the management of PTL in 285 women, across five centers in India. Eligible patients received oral or intravenous tocolytic drugs. Among the pharmacological agents, isoxsuprine was the most frequently used (60.10%), followed by nifedipine (23.83%). Delivery was prolonged for at least 48 hours in 57.76% of patients treated with isoxsuprine, in contrast to 34.78% of those treated with nifedipine, allowing sufficient time for maximal beneficial effect of corticosteroids to those Isoxuprine was administered. Isoxsuprine also resulted in significantly higher mean latency periods (36.77±28.09 vs. 1.44±1.33 days), birth weights (2.25±1.34 vs. 1.07±0.34 kg), and Apgar scores at 5 minutes (7.56±2.36 vs. 4.87±2.10) for cases with gestational ages under 32 weeks ($p<0.0001$). Similar trends were observed in latency periods and Apgar scores for late PTL cases (>32 weeks). In conclusion,

pharmacological treatment, particularly with isoxsuprine, was preferred for managing PTL in India, demonstrating significant improvements in prolonging pregnancy and perinatal outcomes compared to other tocolytics.[20]

Isoxsuprine is commonly used in various clinical scenarios to manage PTL and associated risks.[7] Oral Isoxsuprine 40 mg can be recommended to high-risk patients like short cervix, patients with abdominal pain, patients who are travelling. IV Isoxsuprine in patients with threatened and active PTL followed by oral isoxsuprine as maintenance tocolysis. IV Isoxsuprine in patients with cervical cerclage followed by maintenance tocolysis with oral Isoxuprine 40 mg. In cases of PROM, Isoxsuprine is administered via IV, followed by IM and oral routes, depending on gestational age.

EXPERTS' CONSENSUS

Immediate admission, bed rest, corticosteroid therapy, and magnesium sulfate for neuroprotection are recommended for pregnancies. Once contractions stabilize, patients are considered for transfer to a facility with NICU support. The 80% of panelists preferred isoxsuprine as the first-line drug for managing PTL, with nifedipine favored for its ease of administration and reduced need for monitoring. Atosiban is commonly used in patients with cardiac conditions. Management of PTL is influenced by gestational age at presentation. In-utero transfer is advised when NICU care is available to ensure optimal outcomes for premature neonates. Magnesium sulfate administration is advised between 28-32 weeks for neuroprotection, though some guidelines recommend up to 30 weeks.

MAINTENANCE THERAPY

Maintenance tocolysis, generally defined as extending tocolytic treatment beyond 48 hours, aims to prolong pregnancy to reduce neonatal morbidity and mortality. Preterm contractions persist in 20-30% of women after acute tocolysis, and up to 60% experience recurrence following arrested labor. However, due to inadequate evidence from randomized controlled trials showing improved neonatal outcomes, current guidelines do not recommend maintenance tocolysis.[24]

Most international guidelines do not recommend maintenance tocolysis due to insufficient evidence supporting its effectiveness in prolonging pregnancy or improving neonatal outcomes, however, it continues to be commonly practiced.[5]A survey indicated that 80.8% of obstetric units in Germany perform maintenance tocolysis, despite guidelines advising against it.[25] In Austria, 40.8% of initial tocolysis cycles exceeded 48 hours, with many women receiving multiple cycles.[26] Similarly in France, maintenance tocolysis was found to be prescribed in 50% of cases.[5] This ongoing use, despite established guidelines, highlights a clear disconnect between clinical practice and recommendations.

Discontinuation of tocolysis before term gestation has notable implications for perinatal outcomes. Discontinuing tocolysis before full term is linked to late-preterm births, negative neonatal outcomes, and higher projected healthcare costs. While tocolysis can effectively prolong pregnancy, its cessation has been associated with an increased risk of adverse outcomes. In a retrospective study conducted by Rebarber et al in the US that investigated neonatal outcomes in 4253 healthy, stable singleton pregnancies that electively discontinued tocolysis in the late-preterm period (33.0 to 36.9 weeks of gestation). Despite initial treatment for acute PTL, 58.1% of these women experienced spontaneous PTL and delivered within one week after discontinuing tocolysis.[26] Data were analysed by gestational week at tocolytic discontinuation. Between 33 and 36 weeks of tocolytic discontinuation, there was a notable improvement in pregnancy outcomes. The incidence of delivery before 37 weeks decreased from 75.4% at 33 weeks to 43.2% at 36 weeks. The percentage of low birth weight showed a significant decline from 53.6% at 33 weeks to 9.2% at 36 weeks. Additionally, NICU admissions declined from 44% at 33 weeks to 9.2% at 36 weeks highlighting greater pregnancy prolongation and better neonatal outcomes of maintenance tocolysis. Earlier discontinuation of tocolysis was associated with higher rates of late-preterm birth, low birth weight, NICU admissions, longer neonatal intensive care unit (NICU) stays, and increased NICU charges. Implementing patient management strategies that support prolonged pregnancy could substantially lower the preterm birth rate and lead to significant reductions in newborn care costs.[6]

According to FOGSI guidelines, optimal administration of isoxsuprine for maintenance therapy yields superior fetal and maternal outcomes.[16]

A study by Jaju et al reported 100% efficacy at 24- and 48-hours post-administration (IV/IM). When continued at 40 mg twice daily until 37 weeks, the mean latency period was 58.5 days, with 90% of patients reaching 37 weeks of gestation. No congenital anomalies or fetal infections were observed, with a mean birth weight of 2.7 kg and Apgar scores of 7.5 and 9.2 at 1 and 5 minutes, respectively. Common side effects included tachycardia and vomiting; both were managed by dose adjustment. No ADRs were reported with use of oral isoxsuprine maintenance therapy. The number of infants requiring NICU admission (2%) were significantly lower than NICU admissions reported by previous studies. Overall, isoxsuprine was found to be an effective and well tolerated agent when used as maintenance tocolysis.[27]

EXPERTS' CONSENSUS

Isoxsuprine as maintenance tocolysis has been associated with improved perinatal outcomes, including lesser incidence of NICU admission, improved birth weight outcomes, and extended latency periods. There is a possibility of spontaneous recurrence of PTL after the

cessation of active labor therapy, highlighting the importance of establishing maintenance therapy. Maintenance therapy is beneficial for patients with cervical cerclage, as well as those experiencing threatened or active PTL. Isoxsuprine can be administered in a dosage of 40 mg once daily at bedtime to minimize side effects or in divided doses of 30-40 mg to effectively manage potential side effects.

CONCLUSION

PTB remains a critical global health issue, significantly impacting neonatal and under-five mortality rates. The management of PTL primarily involves tocolytic therapy which is aimed at inhibiting uterine contractions and prolonging gestation. Among the various tocolytic agents available, isoxsuprine is preferred in acute PTL management. Its ability to induce relaxation of uterine smooth muscle has made it a widely utilized option in managing PTL and approved in FOGSI guidelines. Studies indicate that oral isoxsuprine as a maintenance tocolysis is an effective and well-tolerated treatment for delaying preterm delivery and achieving favorable perinatal outcomes. Its use as both an initial treatment and as maintenance therapy has been associated with better maternal and perinatal outcomes in PTL management. The ABM with expert obstetricians reaffirmed the critical role of isoxsuprine in prolonging pregnancy following episodes of PTL.

The effective management of PTL with use of isoxsuprine in acute and maintenance phase is vital for prolonging gestation and improving perinatal health outcomes.

ACKNOWLEDGEMENTS

The authors would like to thank to thank Parv Enterprise (Indyte).

Funding: Funding sources by Abbott India Ltd.
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Mane S, Singh A. Role of isoxsuprine in acute and maintenance tocolysis. Int J Reprod Contracept Obstet Gynecol 2025;14:305-11.