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Review Article

Role of isoxsuprine as a tocolytic agent in the management of preterm labor in Indian clinical practice

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ABSTRACT

Preterm labor (PTL) is one of the prime etiological factors responsible for neonatal disease burden and fatality. Despite recent advances in neonatal care and obstetrics, the occurrence of PTL is increasing, and women who have previously experienced spontaneous PTL are more susceptible to PTL in the future. Currently, PTL is diagnosed based on regular uterine contractions, their frequency, and associated cervical changes. Antenatal corticosteroids and magnesium sulfate interventions can improve neonatal outcomes. Tocolytic medications can temporarily delay delivery to facilitate the administration of corticosteroids. Isoxsuprine is a preferred tocolytic agent because it significantly increases the average latency period, delays delivery by >48 hours, and is associated with improved perinatal outcomes. This review examines recommendations from expert gynecologists for the management of PTL in the Indian clinical setting. The experts opined that intravenous administration with Isoxsuprine provides the advantage of dose titration, thereby minimizing potential side effects. Moreover, continuation of oral isoxsuprine till 37 weeks as maintenance therapy was advised as per literature evidence and experts' clinical experience. Furthermore, concomitant administration of nifedipine and magnesium sulfate was not recommended as this can lead to neuromuscular blockade and fatal respiratory arrest, due to the action of both molecules on the blockage of calcium channels. The experts also emphasized the significance of considering individual experiences with various treatment options and identified specific obstacles and difficulties related to the utilization of isoxsuprine as a tocolytic agent, thereby offering valuable insights into potential approaches to overcome these challenges.

Keywords: Tocolytics, Isoxsuprine, Premature birth

INTRODUCTION

The American college of obstetricians and gynecologists (ACOG) defines PTL as the occurrence of consistent uterine contractions at a rate of four contractions per 20 minutes, along with progressive cervical dilatation (of at least 2 cm) and effacement, before completing 37 weeks of gestation.[1]

PTL can be classified as threatened PTL (uterine contractions and no cervical changes), diagnosed PTL (uterine contractions with cervical dilatation of <4 cm), and established PTL (uterine contractions with cervical dilatation of >4 cm).[2]

Preterm birth (PTB) is one of the most frequent causes of newborn fatalities (occurring within four weeks of life).[3] Despite recent advances in obstetric and neonatal care, the incidence of PTB is increasing. In 2020, WHO estimated the rate of PTB to be 4-16% globally. The prevalence of PTL is considerably high in India (up to 23.3%), and PTB rates range from 10% to 69%.[4]

Assisted reproductive technology (ART), which has been increasingly used for conception in recent times, is a

significant risk factor for PTL. This can be attributed to the association of ART with multiple gestations.[5] In the PTL after assisted reproductive techniques (PLART) study, which was designed to compare adverse pregnancy outcomes after ART or spontaneous conceptions with a focus on the incidence of PTB, it was found that the incidence of PTB was ~3-fold higher with ART pregnancies compared with spontaneous pregnancies.[6]

Efforts to reduce the impact of PTB involve two main approaches, namely, prevention and care. According to the guidelines set by the ACOG, PTL should be managed via prophylactic measures by administering pharmacological therapy to prolong delivery and reduce the risk of infection in neonates.[7]

Tocolytic therapy plays a crucial role in preventing PTL by inhibiting uterine contractions and promoting relaxation of the uterine myometrium by various mechanisms. By delaying preterm delivery, tocolytics provide an opportunity for the sequential administration of antenatal corticosteroids and magnesium sulfate. Corticosteroids help in the maturation of fetal lungs and ensure fetal well-being, whereas magnesium sulfate facilitates fetal neuroprotection and optimal outcomes.[8]

Globally, various agents are employed as tocolytics for managing PTL.[8] However, in India, only isoxsuprine, ritodrine (betamimetic drugs), and atosiban (oxytocin receptor antagonist) have been approved by the central drugs standard control organisation (CDSCO).[9]

Isoxsuprine is the first β-adrenergic agonist utilized to inhibit PTL in India and has been available and widely used for the last six decades.[10,11] It increases the average latency period, delays delivery by >48 hours, and improves perinatal outcomes.[12]

This comprehensive review explores the recommendations for the management of PTL from a panel of expert gynecologists across India and examines the current clinical practices and treatment objectives. Additionally, the experts' insights on the obstacles and difficulties related to using isoxsuprine as a tocolytic agent and potential approaches to overcome these challenges are also discussed.

Two advisory board meetings (ABMs) were conducted in February and March 2023, with an expert panel of 22 experts qualified in obstetrics and gynecology. At the ABMs, the experts discussed the current treatment goals and individual clinical experiences for the management of PTL. The experts addressed various barriers/challenges with the use of isoxsuprine and their remediation. 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." The current guidelines for PTL management were also critically reviewed, and a descriptive analysis of the literature and expert opinions are summarized below.

ETIOLOGY, PATHOPHYSIOLOGY, AND COMPLICATIONS OF PTL

PTL can be influenced by various factors such as stress, placental detachment, placenta previa, drug misuse, history of previous PTB or abortion, environmental factors, inadequate prenatal care, maternal age <18 years and >40 years, smoking, poor nutrition, vaginal bleeding, low body mass index, restricted fetal growth, fetal anomalies, polyhydramnios, oligohydramnios, and premature placental rupture of membranes (pPROMs).[8,13] A meta-analysis involving 55,197 women concluded that a history of spontaneous PTB was associated with a 30% risk of recurrent PTB in subsequent pregnancies.[14]

PTL is often associated with fetal inflammatory response syndrome, which is triggered by factors like chorioamnionitis, decidual hemorrhage, cervical insufficiency, uterine distension, infections, inflammation, and maternal emotional state and distress.[15]

It is hypothesized that a "parturition cascade" plays a part in triggering PTL by involving the release of cortisol and premature activation of proinflammatory pathways (cytokines and prostaglandins) in the uterus. At the molecular level, progesterone and proinflammatory markers collectively regulate the onset of childbirth.[16]

PTL has been linked to an elevated risk of cardiovascular mortality and morbidity in the child, often occurring years after childbirth, although the exact reasons for this association remain unclear.[17] According to the fetal origins hypothesis, hypertension, coronary heart disease, stroke, and type 2 diabetes result from suboptimal nutrition during infancy and fetal development. The Barker hypothesis, proposing the developmental origins of health and disease theory, suggests that adverse conditions during fetal development, such as PTB, can result in long-term health issues. PTB associated with suboptimal intrauterine conditions and stressors increases the risk of chronic diseases in adulthood. Thus, PTB may increase the risk of cardiovascular diseases, diabetes, hypertension, and neurodevelopmental disorders.[18]

Suboptimal prenatal growth and low birth weight increase the vulnerability of the child to environmental factors in adulthood, linking them to health issues.[18] In addition, PTL and PTB are associated with adverse neurodevelopmental outcomes, such as diminished intellectual capacities, motor impairments, cerebral palsy, and visual and auditory disabilities. The risks of these outcomes tend to increase with decreasing gestational age.[15]

RISK FACTORS FOR PTL

The risk factors for PTL and PTB can be classified as maternal, current pregnancy, obstetric, or modifiable and

non-modifiable factors. The risk of PTB differs based on various risk factors in the Indian population, with the highest risk associated with gestational hypertension (25%), diabetes (9%), anemia (55%), previous history of a medically terminated pregnancy or miscarriage, fibroids, urinary tract infection (UTI), ART, insufficient antenatal care, infections during pregnancy, and previous history of preterm birth.[4,12,14,19,20]

Expert consensus

The experts agreed that the prevalence of PTL in Indian clinical practice ranges between 10% and 15% The experts mentioned that the predominant risk factor for PTL is a previous history of preterm birth. Experts opined that PTB cannot always be predicted as patients without risk factors may also experience PTL.

CLINICAL PRESENTATION OF PTL

PTL can set in anytime between 20 and 36 weeks of pregnancy; it usually manifests as contractions occurring every 10 minutes (or more frequently, causing the uterine muscles to contract) and changes in vaginal discharge, including fluid leakage or vaginal bleeding.[2] Additionally, there may be the sensation of pressure in the pelvic (hip) area, with dull, low backache and abdominal cramps. Physical examination may reveal cervical effacement or dilatation of at least 2 cm.[21]

One condition that can mimic PTL is Braxton Hicks contractions, also known as "false labor." These contractions are inconsistent and often painless and can confuse patients. Proper assessment and monitoring are essential to differentiate Braxton Hicks contractions from true PTL.[22]

Other conditions that may mimic PTL include UTIs, vaginal infections, and gastrointestinal issues. UTIs can cause pelvic discomfort and increased frequency of urination, which can be mistaken for PTL symptoms. Certain gastrointestinal symptoms like gastritis, constipation, and diarrhea can also mimic PTL. Similarly, vaginal infections, such as bacterial vaginosis or yeast infections, can induce vaginal discharge and irritation, which may be misinterpreted as signs of PTL. Accurate diagnosis through appropriate testing is crucial to differentiate these conditions from true PTL.[23]

Expert consensus

The experts unanimously agreed that the common presenting symptoms of PTL contractions may be mimicked by gastrointestinal symptoms like gastritis, constipation, and diarrhea, or symptoms of UTIs. According to the experts, false labor pains/Braxton Hicks contractions differ from PTL contractions as they are irregular, painless, have no associated cervical changes, and usually subside on taking analgesics.

DIAGNOSIS OF PTL

It can be diagnosed by recording complete patient history, inclusive of pregnancy and PTB history, assessment of progression of uterine contractions, infections, fetal anomalies and uterine/cervical anomalies.[3]

Physical examination involves assessing the general status of the patient, the patient's weight, vital signs, temperature, and pulse rate (both may be elevated in the presence of infection), respiratory rate, and blood pressure. The fetal movement must also be monitored.[3] Assessing the firmness of the abdomen, abdominal tenderness, fetal size, and fetal position can provide important information about the progression of labor, the well-being of the fetus, and any potential complications. The intensity, frequency, and duration of contractions must be assessed.[15] Cardiotocography offers important insights into fetal heart rate patterns, particularly in high-risk pregnancies.[24] Digital cervical assessment can be utilized to evaluate the cervix, monitor cervical dilatation and effacement, and identify potential risks for PTL.[3] Finally, a speculum examination helps to examine the cervix; accumulation of amniotic fluid in the posterior fornix of the vagina may be an indication of pPROM.[3] Fetal fibronectin is also used for diagnosis; its absence in the upper vaginal tract is an excellent negative predictor for the onset of labor within 7 days (97%-99.5%).[3]

CHALLENGES ASSOCIATED WITH SCREENING FOR PTL

Although numerous sociodemographic, nutritional, medical, obstetric, and environmental factors have been identified as potential risk factors for spontaneous PTB, the exact causes of PTB remain unclear.[25] Meta-analyses of observational studies are limited, and they may not fully account for potential confounding factors.[25]

The presence of a shortened cervical length of <25 mm (as evaluated by transvaginal ultrasound [TVUS]) at 16-24 weeks of gestation is indicative of PTB.[26,15,3] Women who are referred for cervical length screening at 16-24 weeks of gestation are those who have a history of preterm birth at 16–34 weeks of gestation, a pregnancy loss in the mid-trimester, pPROM in previous pregnancies, and a history of large loop excision of the transformation zone (LLETZ) of a depth of >10 mm.[2]

The fetal fibronectin (fFN) test is valuable for predicting the likelihood of PTB.[27] A negative value for fFN implies negligible risk of PTB and levels of >200 ng are a cut-off for considering an in-utero transfer and antenatal corticosteroids. Additionally, fFN is an objective tool for counseling patients and ensuring patient compliance.[2,8]

Expert consensus

The experts emphasized the importance of cervical length assessment at 16–24 weeks of gestation using TVUS.

Pregnant women at a high risk of PTL should undergo regular cervical monitoring in the second trimester until 24 weeks. Although regular cervical assessment is recommended, the risk of infections associated with repeated pelvic examinations should be considered.

PREVENTION OF PTL

During the initial evaluation, TVUS may be conducted as part of the comprehensive care provided to women to determine the cervical length and predict the risk of PTB.[28] A cervical length of <25 mm as detected via ultrasound would require the consideration of the benefits and risks of progesterone administered vaginally, cervical cerclage, and expectant management.[2] Additionally, according to the 2023 ACOG recommendations, vaginal progesterone may be used in women with a previous record of PTB.[29] There is a need to understand the requirement for prevention and treatment strategies. However, these strategies have been found to play a limited role in the treatment of PTL.

MANAGEMENT OF PTL

According to experts, PTL management includes bed rest with the head resting in a low position and administration of tocolytic therapy along with corticosteroids and magnesium sulfate to promote fetal lung maturity and neuroprotection. Patients with short cervices (if identified early during pregnancy) may undergo cerclage placement. All the experts were aware of and strongly opined to follow federation of obstetric and gynaecological societies of India (FOGSI) guidelines for the management of PTL.[2]

The administration of corticosteroids has been advocated by the ACOG as a primary treatment option for improving neonatal outcomes in women at high risk of PTL.[30] Betamethasone and dexamethasone are commonly used as antenatal treatment options in pregnant women (between the 24th and 34th weeks of gestation) to delay PTL and for fetal lung maturity during the management of PTL.[7] A Cochrane meta-analysis concluded that administering a single course of antenatal corticosteroids promotes fetal organ maturation and reduces neonatal mortality.[30]

The ACOG guidelines support the use of tocolytic therapy to achieve short-term delay of pregnancy by a maximum of 48 hours.[7] Multiple meta-analyses and studies have shown that tocolytic agents can effectively delay PTB for up to 48 hours and potentially extend pregnancy by up to seven days.[8]

Expert consensus

All the experts opined that they followed the FOGSI guidelines for the management of PTL.

TOCOLYTICS IN THE MANAGEMENT OF PTL

Tocolysis is indicated in cases of PTL before the 34th week of gestation, depending on the specific pregnancy scenario. FOGSI guidelines recommend the utilization of tocolytics to prolong the gestational period, enable the administration of corticosteroids and magnesium sulfate if needed, reduce chances of intraventricular hemorrhage, reduce the severity of fetal respiratory distress syndrome, and facilitate transferring the patient to a specialized medical center when needed.[2,8]

The ACOG guidelines recommend several drugs as first-line tocolytics, such as β-adrenergic receptor agonists (betamimetics), oxytocin receptor antagonists, calcium channel blockers, non-steroidal anti-inflammatory drugs (NSAIDs), nitric oxide donors, and magnesium sulfate.

The various tocolytic agents used in clinical practice are summarized in Table 1.[8,31–33]

Table 1: Overview of various tocolytic agents used for the treatment of PTL.

Drug class	Examples	Mechanism of action	Dosage	Side effects
Betamimetics	Isoxsuprine ritodrine	Activates intracellular enzymes, reduces the levels of free intracellular Ca^{++}, and inhibits the activation of myosin light chain kinase Reduces interaction of actin and myosin, leading to smooth muscle relaxation	Isoxsuprine: IV infusion of 4 ampoules in 500 mL 5% dextrose/ Ringer lactate IM administration is done only if facilities for IV administration are unavailable till symptom remission occurs. An hourly/bi-hourly dose of 10 mg is recommended for symptoms of PTL. Oral administration can be done after IV or IM administration provided uterine activity has completely subsided. It is administered in a maintenance dose; as a daily divided dose of 60-80 mg	Hypotension, tachycardia, nausea, and vomiting

Continued.

Drug class	Examples	Mechanism of action	Dosage	Side effects
Calcium channel blockers	Nifedipine	Nifedipine blocks the entry of Ca^{++} inside the cell	Oral administration of 10-20 mg every 3-6 hours	Hypotension, headache, flushing, and nausea. Combined therapy with magnesium sulfate should be avoided
Oxytocin receptor antagonists	Atosiban	Blocks myometrial oxytocin receptors. It inhibits the release of prostaglandins and Ca^{++}, thereby inhibiting myometrial contractions	IV atosiban administration is carried out in three consecutive stages: Initial bolus of 6.75 mg/0.9 mL atosiban solution, followed by continuous high-dose infusion of a 37.5 mg/5 mL concentrate solution of atosiban for 3 hours at 300 µg/min, and then an infusion of a low-dose atosiban of 37.5 mg/5 mL concentrate solution for 45 hours at 100 µg/min. The treatment duration should be within 48 hours. The total dose of atosiban given should not be more than 330.75 mg	Nausea, vomiting, and chest pain (rarely)
NSAIDs	Indomethacin	Reduces the synthesis of prostaglandins, thereby reducing intracellular free Ca++, the activation of myosin light chain kinase, and uterine contractions	A loading dose of 50 mg orally followed by 25 mg every 6 hours for 48 hours	Heartburn, asthma, GI bleeding, thrombocytopenia, renal injury, and platelet dysfunction
Nitric oxide donors	GTN	Smooth muscle relaxant	Patches	Cervical ripening and headache

Ca^{++}: Serum calcium, GI: Gastrointestinal, GTN: Glyceryl trinitrate, IM: Intramuscular, IV: Intravenous, NSAIDs: Non-steroidal anti-inflammatory drugs, PTL: Preterm labor.

Each of these drugs has a distinct mechanism of action and carries specific risks and benefits. However, the use of nifedipine in managing PTL is not CDSCO-approved in India.[34] Nifedipine has not been licensed for use in pregnancy or in PTL as per the innovator (expert opinion published in 2014).[35] Among the available pharmacological agents, isoxsuprine is the most preferred tocolytic agent.

The results from a Cochrane systematic review comparing placebo treatment with tocolytic treatment indicated that tocolytic treatment was effective in delaying PTB for 48 hours to 7 days. However, the use of tocolytic drugs was related to a spectrum of adverse effects, varying in severity, when compared with placebo or no treatment.[36]

Expert consensus

For established PTL, the decision to administer tocolytics is based on the progression of cervical effacement. If cervical dilatation is >4 cm with progressive cervical effacement, the patient must be referred to a neonatal intensive care unit, and magnesium sulfate and steroids should be administered. Delivery should be done in the presence of a neonatologist.

Patients with pPROM without an infection should be given tocolytics to allow time for antenatal corticosteroid administration which further helps in achieving fetal lung maturity, and magnesium sulfate is given for neuroprotection as per gestational age. Cervical cerclage is recommended if the cervical length is <25 mm before 24 weeks of gestation. Parenteral tocolysis was recommended postoperatively. Atosiban and isoxsuprine have been approved for use as tocolytic agents by the CDSCO; however, the use of nifedipine has not yet been authorized by the CDSCO.

ISOXSUPRINE

Isoxsuprine is a CDSCO-approved medication that has been in use in India for over six decades. It causes direct relaxation of the vascular smooth muscles and results in peripheral vasodilation. It also induces uterine smooth muscle relaxation. Therefore, it is used for the treatment of dysmenorrhea and PTL.[11] Based on the effectiveness and safety of this drug, FOGSI has developed a treatment algorithm that includes a dosage regimen for isoxsuprine. Isoxsuprine is the most frequently used tocolytic agent. In

a previous study, its use demonstrated successful tocolysis in all patients within 24 hours of its administration, of which 94% underwent vaginal deliveries and a large number of patients completed 37 weeks of gestation as compared to those who delivered before 37 weeks.[10] A systematic review has reported an efficacy rate of approximately 89% for isoxsuprine in the management of PTL when administered via the IV route or as maintenance therapy via intramuscular or oral routes.[32]

According to the revised FOGSI dosage regimen, management of patients using isoxsuprine involves the administration of 40 mg isoxsuprine IV infusion diluted in 500 mL 5% w/v dextrose, with a drop rate set at eight drops per minute (0.04 mg/min).[37] The drop rate should be elevated by eight drops per minute every 15 min till uterine quiescence is achieved, and infusion should be continued for 12 hours. Experts advised to wait at least 15 min before increasing the dose, to allow for the drug to show its effect and to avoid sudden dose escalation, thus preventing subsequent development of adverse effects. Patients who achieve uterine quiescence are then given intramuscular injections of isoxsuprine at a dose of 10 mg every 4 hours for the first 24 hours. Subsequently, maintenance therapy with isoxsuprine using 40 mg sustained-release capsules twice daily is recommended. This maintenance therapy should be continued until delivery or until 37 weeks of pregnancy are completed.[10] Table 2 describes the recommended doses of isoxsuprine based on patient profiles.[2]

Table 2: Patient profiles for using isoxsuprine and their prescribing information.

Diagnosis	Prescribed dosage
Short cervix	Prophylactic cerclage in early pregnancy and progesterone supplementation. A dose of 40 mg oral isoxsuprine can be added until 36 weeks of gestation
Prophylaxis in high-risk patients (patients who complain of pain in abdomen or those who are traveling)	Progesterone supplementation (IM/oral/vaginal) with 40 mg OD isoxsuprine
PTL without cervical changes	IV isoxsuprine followed by 40 mg isoxsuprine OD until 36 weeks of gestation
PTL with cervical changes	IV isoxsuprine followed by IM, and then oral isoxsuprine Maintenance tocolysis: 40 mg isoxsuprine OD until 36 weeks
Patients undergoing cervical cerclage	IV isoxsuprine for 24 hours followed by 40 mg OD for 7–10 days
pPROM	IV isoxsuprine followed by IM and then oral isoxsuprine depending on gestation age

IM: Intramuscular, IV: Intravenous, OD: Once daily, pPROM: Preterm premature rupture of membrane, PTL: Preterm labor.

Isoxsuprine is associated with minimal dose-dependent adverse effects such as nausea, constipation, tachycardia, palpitation, and hypotension, similar to other tocolytic drugs, which can be minimized by dose titration.[10,32] FOGSI guidelines recommend maintenance with isoxsuprine, which has superior fetal and maternal outcomes on optimum administration.[2] A study by Jaju et al, found 100% efficacy at 24 and 48 hours post-administration with isoxsuprine (IV/IM), which when continued at 40 mg twice daily until 37 weeks, was found to have a mean (standard deviation [SD]) latency period of 58.5 (18.5) days in arresting PTL.[10] Overall, 90% of patients reached the gestation period of 37 weeks, while 10% delivered before 37 weeks. No instances of congenital anomalies or fetal infections were observed. Mean (SD) fetal birth weight was 2.7 (0.3) kg and the mean (SD) Apgar score at 1 and 5 minutes was 7.5 (0.6) and 9.2 (0.4), respectively. The most reported side effects experienced by the patients were tachycardia and vomiting, both of which were resolved by adjusting the dosage of isoxsuprine.[10] Upon comparing 10 mg vs. 40 mg maintenance dosage in one of the studies, the mean duration of prolonging pregnancy with the 40 mg dose was found to be 15 days, whereas that with the 10 mg dose was 4 days.[38]

In an Indian multicenter study evaluating practice patterns in the management of PTL, it was found that among 285 women admitted or treated for PTL, isoxsuprine was the most frequently prescribed drug, followed by nifedipine (Table 3). Moreover, delivery was prolonged for a minimum of 48 hours in 57.8% of patients on isoxsuprine as compared to 34.8% of patients on nifedipine.

Table 3: Preterm labor management with tocolytics.[12]

Tocolytic agent	Frequency of use
Isoxsuprine	60%
Nifedipine	24%
Isoxsuprine + nifedipine	9%
Nifedipine + magnesium sulfate	5%
Magnesium sulfate	1%
Isoxsuprine + nifedipine + magnesium sulfate	1%

Expert consensus

For threatened and active PTL, IV isoxsuprine should be administered. However, patients experiencing threatened and active PTL must be shifted to oral isoxsuprine maintenance therapy. Patients with active PTL need to be administered corticosteroids and magnesium sulfate as required according to gestational age. The experts opined that after increasing the drip rate, they wait for 15 minutes to monitor blood pressure and pulse rate and further increase the drip rate. This gradual dose titration helps prevent any potential side effects. Table 4 provides a summary of the pharmacotherapies recommended by the experts for the management of PTL.

Table 4: Expert opinion on the medications used for the management of PTL.

Therapy	Expert opinion
Isoxsuprine	Isoxsuprine is the first-line tocolytic agent used by 80% of the panelists. IV isoxsuprine is the preferred drug for managing active PTL. The IV route of administration provides the advantage of titration to minimize side effects. Dose titration enables personalized treatment, optimizes outcomes, and reduces the occurrence of adverse drug reactions.[39] The IV/IM dose is followed by a 10 mg oral dose of isoxsuprine, 4–5 tablets per day after food, and the patient should be in the left lateral supine position to avoid any side effects. The efficacy of isoxsuprine is 80%–90% based on expert clinical experience. Oral isoxsuprine should be continued until 37 weeks as maintenance therapy in accordance with literature evidence and experts' clinical experience. The 40 mg dose provides better latency and neonatal outcomes compared with the 10 mg dose.
Nifedipine	Nifedipine is preferred by some due to the ease of administration and the need for reduced monitoring. The use of nifedipine has not yet been authorized by the CDSCO for managing PTL. Nifedipine is not licensed for use in pregnancy or in PTL management as per the innovator (expert opinion published in 2014). It is important to note that headaches caused by nifedipine during tocolysis can be concerning as they can be difficult to differentiate from headaches due to imminent eclampsia.
Magnesium sulfate	Magnesium sulfate can be recommended to women likely to undergo PTL for neonatal neuroprotection. Nifedipine and magnesium sulfate should not be administered concomitantly as this can lead to neuromuscular blockade and fatal respiratory arrest, due to the action of both molecules on the blockage of calcium channels. Such interactions have been already reported in the literature. As per guidelines by the Royal College of Obstetricians and Gynaecologists, concomitant administration of nifedipine and magnesium sulfate is relatively contraindicated. FIGO 2021 Good Clinical Practice guidelines recommend the use of magnesium sulfate for neuroprotection in women who are at risk of preterm imminent birth (viability to 30 weeks of gestation). In pregnancies below 32–34 weeks of gestation, the use of magnesium sulfate for neuroprotection of the fetus should be considered.
Atosiban	The experts opined that atosiban is effective and well-tolerated. They also stated that atosiban can be used in cardiac patients such as those with rheumatic heart disease. However, it is expensive. Also, dose titration is complicated and requires constant monitoring.
General	The WHO, FIGO, and FOGSI should continue to develop guidelines pertaining to the use of steroids and tocolytics for improving pregnancy and neonatal outcomes in patients with PTL. As Indian PTL guidelines were last updated in 2019, the panelists suggested reframing and updating the FOGSI guidelines. To further investigate the efficacy of isoxsuprine in PTL management, the experts recommended that key opinion leaders who have significant experience with the drug must be approached for collecting data and conducting studies; this will help establish the effectiveness of isoxsuprine and contribute to the existing body of research in this area.

CDSCO: Central drugs standard control organization, FIGO: International federation of gynecology and obstetrics, FOGSI: Federation of obstetric and gynecological societies of India, IM: Intramuscular, IV: Intravenous, pPROM: Preterm premature rupture of membrane, PTL: Preterm labor, WHO: World health organization.

CONCLUSION

The existing clinical practices and treatment goals in managing PTL in India have been reviewed and the importance of understanding the individual experiences of experts with different tocolytic agents has been emphasized. Isoxsuprine is approved by the CDSCO and is included as a treatment option in the FOGSI guidelines for PTL management; hence, clinicians often prefer isoxsuprine as a first line tocolytic therapy. Significant improvements have been noted in perinatal outcomes in patients on isoxsuprine in terms of the mean latency period and prolonging delivery beyond 48 hours when compared with other drugs. Additionally, tocolytic agents such as isoxsuprine are safe and effective in management of PTB.

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