Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS
ROYAL COLLEGE OF PHYSICIANS OF IRELAND

CLINICAL PRACTICE GUIDELINE

TOCOLYTIC TREATMENT IN PREGNANCY

Institute of Obstetricians and Gynaecologists,
Royal College of Physicians of Ireland
And
Directorate of Strategy and Clinical Care
Health Service Executive

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Key Recommendations

1. *Antenatal corticosteroids* significantly reduce the incidence and severity of neonatal respiratory distress syndrome and are recommended as a single course in women at risk of delivery between 24 and 34 weeks' gestation. Therefore, they should be used in the setting of preterm labour (PTL).

2. No particular tocolytic agent has been proven optimal for PTL. Tocolytic agents have not been proven to reduce perinatal or neonatal mortality; therefore it is also reasonable not to use tocolytics in the setting of PTL.

3. The oxytocin receptor antagonist Atosiban has been specifically designed to treat PTL with women incurring fewer side effects than the previously popular beta agonists.

4. Both calcium channel blockers (Nifedipine) and Atosiban have similar efficacy in delaying pregnancy for up to 7 days but nifedipine may be more likely to delay delivery for 48 hours.

5. Maintenance treatment with tocolytic drugs or repeat tocolytic treatment does not appear to improve perinatal outcome and therefore is not recommended.

6. Use of multiple tocolytic agents should be avoided due to the risk of increasing adverse effects. Particular caution should be exercised if tocolytics are considered in multiple gestations due to the increased risk of adverse effects. Particular caution should also be exercised if nifedipine is used in combination with magnesium sulphate, either in the setting of tocolysis, or if magnesium is being used for neuroprotection.

7. When managing a woman with PTL at a smaller maternity unit, if the woman is stable and not imminently delivering, consideration should be given to transfer of the woman to a tertiary referral centre with appropriate neonatal facilities.

8. Senior medical staff should be involved in the decision as to when and whether to transfer a woman with suspected PTL.

1. Purpose and Scope

The purpose of this guideline is to describe the role of tocolytic medications in the setting of preterm labour (PTL).

These guidelines are intended for healthcare professionals, particularly those in training, who are working in HSE-funded obstetric and gynaecological services. They are designed to guide clinical judgment but not replace it. In individual cases a healthcare professional may, after careful consideration, decide not to follow a guideline if it is deemed to be in the best interests of the woman.

2. Background and Introduction

Premature (or preterm) birth, defined as birth at less than 37+0 weeks' gestation, is the leading cause of neonatal mortality and morbidity in economically advantaged countries. The incidence of preterm birth in Ireland is 4.4%, compared with 12% in the United States. Premature birth is responsible for between 75 and 90% of neonatal mortalities, not due to congenital anomalies, and is also responsible for up to 50% of cases of neurodevelopmental disability (Hack and Fanaroff, 1999). The majority of cases of adverse outcome occur in those cases under 34 weeks' gestation. There is now growing evidence that the moderately preterm group (delivered between 32+0 to 37+0) are also at increased risk of infant death (Moser et al, 2007; Kramer et al, 2000).

Identifying those women with PTL who will actually go on to preterm delivery is very difficult. PTL may resolve spontaneously in up to 30% of cases (Lewit et al, 1995), with less than 10% of women delivering within 7 days of an initial diagnosis of PTL (Fuchs et al, 2004).

Where there may be benefit in delaying delivery (e.g. at a very preterm gestational age), and where there is no obstetric indication to expedite delivery in a pregnancy < 34 weeks gestation, the primary objective of delaying delivery with tocolytics is to optimise fetal lung maturation using antenatal corticosteroids. The other main objective of tocolytic use in this setting is to arrange for maternal transfer from a regional to a tertiary level medical centre with appropriate neonatal care facilities.

The aetiology of PTL is diverse, including infection, antepartum haemorrhage, and multiple pregnancy, although in many cases there is no clinically obvious cause. Preterm delivery may be inevitable in some cases of PTL, owing to the multifactorial array of possible pathologies. However recognizing the symptoms and signs of PTL (*secondary prevention*) is key to prompt the administration of corticosteroids, administration of magnesium sulphate for fetal neuroprotection, and enable maternal transport to a tertiary referral centre if required (*tertiary prevention*).

Primary prevention of those at high risk of PTL, (such as shortened cervix after LLETZ), is outside the scope of this guideline. Ideally a clinical test with a high positive predictive value to determine those women with PTL who are highly likely to deliver preterm, would enable more streamlined care for those women at risk (Honest et al, 2009), thereby preventing over-treatment with tocolytic agents. Fetal fibronectin testing and measurements of cervical length have been evaluated for this indication; however their positive predictive values are poor, while their strong negative predictive values may be helpful in avoiding unnecessary interventions (Mathews and Mac Dorman, 2010; Mac Dorman et al, 2007).

The diagnosis of PTL is based on clinical criteria of regular uterine contractions, together with documented cervical dilatation, with or without rupture of the fetal membranes after 20 weeks' and before 37 weeks of pregnancy (WHO, 1977). The term 'threatened PTL' is often used for uterine contractions but without cervical change. Previous conservative treatments such as bed rest and pelvic rest have not proven to be effective in avoiding progression of PTL to actual preterm delivery (Sosa et al, 2004).

Pharmacological agents- namely tocolytics (from the Greek *tokos*, childbirth, and *lytic*, capable of dissolving) – were first recognised for their ability to suppress uterine contractions in 1959, when Hall et al observed the tocolytic effects of magnesium sulphate (Hall et al, 1959). Following this in 1961, the beta-agonist isoxuprine was described as a first-line tocolytic (Bishop and Woutersz, 1961). The wide range of tocolytics for use in clinical practice reflects the lack of a single *ideal* agent available. Five classes of tocolytic agents have been described:

- betamimetics
- calcium channel blockers
- oxytocin receptor antagonists
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- magnesium sulphate

There is no reliable national data on current use of each particular tocolytic class; however it is likely that oxytocin receptor antagonists (*Atosiban*) specifically developed for use as a tocolytic, and calcium channel blockers (*Nifedipine*) are the most widely used in clinical practice.

Rationale for Tocolytics

- There have been significant improvements in the care of the premature infant, with neonatal survival rates ranging from 8% at 23 weeks' to 74% at 26 weeks' gestation. Infants 'outborn' of a tertiary center and subsequently transferred have a significantly greater risk of death due to severe intraventricular hemorrhage, respiratory distress syndrome, patent ductus arteriosus, and nosocomial infection than infants 'inborn' in tertiary care centers (Chien et al, 2001) . A recent retrospective population based cohort study (*Paediatrics* August 2012) concluded

that neonatal mortality was significantly reduced when high-risk premature infants are born in hospitals with high-level neonatal intensive care units (NICU) than in other hospital settings (Lorch et al, 2012). Delaying immediate delivery to subsequently facilitate transport to appropriate high-level care centers is therefore likely to improve neonatal outcomes.

- The administration of antenatal corticosteroids to a woman at risk of imminent preterm birth is associated with a significant reduction in perinatal morbidity and mortality (Crowley, 1995; Crowther et al, 2002; Crowther et al, 2011), with a significant reduction in respiratory distress syndrome (relative risk [RR] 0.66; 95% confidence interval [CI] 0.59-0.73), intracranial haemorrhage (RR 0.54; 95% CI 0.43-0.69), necrotising enterocolitis (RR 0.46; 95% CI 0.29-0.74), and death (RR 0.69; 95% CI 0.58-0.81) in pregnancies delivering between 48 hours and 7 days (Roberts and Dalziel, 2006).

- Tocolytic agents are effective for up to 48 hours and may prolong pregnancy for up to 7 days, but this has not been equated to a significant reduction in perinatal morbidity or mortality (Anotayanonth et al, 2004). Therefore it is considered clinically reasonable both to use or not to use tocolytics, depending on the clinical scenario. It is *reasonable* to administer tocolytics to optimize time in-utero, so as to allow for the administration of corticosteroids and to facilitate transfer of the patient to a tertiary referral centre.

Careful selection of those women in PTL, where it is suitable and safe to consider tocolytic treatment, is the responsibility of the health care team, as for some women (e.g. those with chorioamnionitis or placental abruption), prolonging the pregnancy may be contraindicated.

Other proposed interventions to prolong pregnancy and improve neonatal outcome, such as antibiotics to treat intrauterine bacterial infection, or cervical cerclage for short cervix, are outside the scope of this guideline. It is essential that any potential underlying cause for PTL be excluded by careful evaluation of the woman and fetus before appropriate treatment options are considered (Appendix 1).

3. Methodology

Medline, EMBASE and Cochrane Database of Systematic Reviews were searched using terms relating to 'preterm labour', 'preterm labour', 'tocolysis', 'antenatal corticosteroids', 'beta-agonist and preterm labour', 'calcium-channel blocker and preterm labour', 'non-steroidal anti-inflammatories and preterm labour', 'magnesium sulphate and preterm labour', 'oxytocin receptor antagonist and preterm labour'.

Searches were limited to humans and restricted to the titles of English language articles published between 1999 to 2012. Relevant meta-analyses, systematic reviews, intervention and observational studies were

reviewed. Guidelines reviewed included RCOG Green-top Guideline No. 1b Tocolysis for Women in Preterm Labour, Feb 2011; ACOG Practice Bulletin No. 127 on Management of Preterm Labor June 2012.

The principal guideline developers were Dr. Siglinde Mullers and Prof. Fergal Malone.

The guideline was peer-reviewed by: Dr. Paul Hughes, Dr. Alan Finan, and Prof. Louise Kenny. Finally, the guideline was reviewed and endorsed by the Programme's Clinical Advisory Group and National Working Party.

4. Clinical Guideline on Tocolytic Treatment in Pregnancy

4.1 Diagnosis of PTL/ Threatened PTL

The diagnosis of preterm labour (PTL) is based on clinical criteria of documented regular uterine contractions, together with cervical dilatation, with or without rupture of fetal membranes (20 weeks to 37 weeks' gestation) (WHO, 1977).

Women presenting at less than 37 weeks gestation with PTL should be triaged as a priority and evaluated by careful clinical assessment by an experienced clinician to outrule possible underlying causes of PTL. Streamlined medical care and decisions on appropriate management is therefore crucial.

Intrauterine infection, placental abruption, and preterm premature rupture of membranes should be considered before a decision to begin tocolytic therapy is made. In some circumstances delaying delivery may be harmful to both mother and fetus, whereas expediting delivery may be more appropriate. A cardiotocograph is typically performed on admission, as abnormalities of fetal heart rate patterns in the setting of PTL will usually contraindicate subsequent tocolytic therapy (Raybum et al, 1987).

The term 'Threatened PTL' (TPTL) is often reserved in the clinical setting for documented uterine contractions but without cervical change. Women with TPTL generally do not require tocolysis (Crowther et al, 2011). However it reasonable to offer hospital admission and consideration of corticosteroid therapy if suspicion of progression to true PTL is high.

The decision to administer a tocolytic agent for PTL should be discussed with a senior obstetrician.

4.2 Indications for use of Tocolytic therapy

Tocolytic therapy may be considered for women with confirmed PTL between 24 and 34 weeks' gestation, where there is no contraindication to their use, and where a delay in delivery of the newborn is likely to improve neonatal outcome. Those most likely to benefit are those in very early PTL (less than 28 weeks' gestation), where it may be prudent to gain time to allow for completion of corticosteroids, and to allow for safe in-utero transfer from a regional to tertiary-level hospitals with appropriate NICU facilities (Lorch et al, 2012).

4.3 Contraindications to Tocolytic therapy

Tocolytic agents are contraindicated where prolonging the pregnancy could cause harm to mother or fetus. The aetiology of PTL is diverse, and in select cases, *expediting delivery* may be justified (e.g. chorioamnionitis). Contraindications to tocolysis include:

- Chorioamnionitis/ sepsis
- Significant antepartum haemorrhage, such as placental abruption/ active vaginal bleeding
- Advanced cervical dilatation
- Abnormal CTG suggesting non-reassuring fetal status
- Placental insufficiency
- Pre-eclampsia/ eclampsia
- Lethal congenital/chromosomal malformation
- Intrauterine fetal demise
- Maternal allergy to specific tocolytic agents, or where tocolytics are contraindicated with specific co-morbidities (e.g. beta-agonists should not be given in case of cardiac disease)
- Gestational ages < 24 weeks or > 33+6 weeks

4.4 Relative contraindications to tocolysis:

In some circumstances, relative contraindications to tocolytic use may be present, but it may still be reasonable to administer tocolytics. The risk-benefit balance in such select cases should be carefully considered by a senior obstetrician prior to the decision to proceed with tocolysis. Below are some circumstances where treatment with tocolysis may proceed with caution:

- Preterm premature rupture of membranes (PPROM) in the absence of intrauterine infection. However, it should be noted that it can be very difficult to confidently exclude the presence of co-existing intrauterine infection. Often, the only clinical feature of intrauterine infection in the setting of PPROM may be contractions.
- Mild antepartum haemorrhage secondary to placenta praevia.

- Intrauterine growth restriction
- Multiple pregnancy. Tocolytics should be used with caution in any clinical setting in which pulmonary oedema is likely.
- Liver or renal disease.

4.5 Choice of Tocolytic

4.5.1: Atosiban (*Tractocile*):

Atosiban was specifically developed as a tocolytic and is a modified form of oxytocin that competitively blocks uterine oxytocin receptors, therefore halting uterine contractions. Studies have suggested a statistically significant increase in the number of women with an ongoing pregnancy within 7 days of commencing atosiban treatment (Gyetvai et al, 1999; Romero et al, 2000). Its use is widespread due to its low incidence of maternal and fetal adverse effects. Fewer maternal drug reactions have been associated with atosiban when compared with other tocolytics (Papatsonis et al, 2005). It is licensed for use as a tocolytic between 24 0/7 and 33 6/7 weeks' gestation, and is given as an initial intravenous bolus followed by maintenance intravenous therapy (see dose regimes below), for a total of 48 hours.

However, a recent Cochrane review (Papatsonis et al, 2005) did not demonstrate any superiority of atosiban over beta-agonists or placebo in terms of tocolytic efficacy or infant outcomes. Compared with beta-agonists, there were more atosiban-exposed infants with birth weights under 1500 gms (RR 1.96; 95% CI 1.15 to 3.35, 2 trials, 575 infants), and no overall clear benefit on in perinatal or neonatal outcomes. In one trial of 583 infants atosiban was associated with an increase in infant deaths at 12 months of age compared with placebo (RR 6.15; 95% CI 1.39 to 27.22), however there was an imbalance of groups at randomisation; with more women at lower gestational ages (P = 0.008) and more advanced labour in the atosiban group (Romero et al, 2000). Given the lack of clear overall clinical benefit with atosiban, it is also considered reasonable not to use atosiban in clinical practice.

Recommended atosiban dosage regime

Atosiban is given intravenously in three successive stages:

- **Initial intravenous injection of 6.75mg in 0.9ml slowly injected over one minute**
- **A continuous infusion at a rate of 24 ml/hr up to 3 hours**
- **A continuous infusion at a rate of 8ml/hr up to 45 hours**

Total duration of the treatment should not exceed more than 48 hours. Further cycles of treatment can be used should contractions recur, and no more than three retreatments are recommended during a pregnancy. However, given that the principal benefit of tocolytic use is to allow for corticosteroid administration and transfer of the mother to a tertiary-level centre, the role of repeat cycles of treatment becomes increasingly difficult to justify.

Atosiban Side Effects:

- Common side effects (affecting less than 1 in 10):
  - Headache, dizziness, hot flushes, vomiting, tachycardia, hypotension, reaction at site of injection, hyperglycaemia
- Uncommon side effects (affecting less than 1 in 100 people)
  - Fever, insomnia, itching, rash
- Rare side effects (affecting less than 1 in 1,000 people)
  - Postpartum haemorrhage
  - Serious allergic reactions

4.5.2: Calcium Channel Blockers:

Calcium channel blockers reduce intra-cellular calcium by blocking trans-membrane calcium transport. While its use for PTL is unlicensed (British National Formulary), it is commonly used due to ease of oral administration and low cost. A review of ten trials, including 1,029 women, comparing oral nifedipine with the beta agonist ritodrine, nifedipine appeared to be more effective in delaying delivery before 34

weeks gestation and for at least 7 days until delivery (RCOG 25, 26) with a lower side effect profile than beta agonists.

A Cochrane review (King et al, 2003) suggested that calcium channel blockers (nifedipine) are associated with statistically and clinically significant better neonatal outcome and fewer maternal side-effects than any other tocolytic. However, a randomised comparison of nifedipine with atosiban is not available. Calcium channel blockers should be used with caution in women with cardiovascular disease due to the risk of cardiac failure.

Nifedipine has been used in select clinical settings before viability to inhibit uterine contractions, such as intra-abdominal surgery. These interventions have not been proven to be effective (Allen et al, 1989; Hunt et al, 1989).

Relative contraindications to use of nifedipine include concurrent use of beta-agonists and magnesium sulphate due to the risk of hypotension. Particular caution should therefore be exercised if magnesium sulphate is administered at the same time as nifedipine, either when magnesium is being used for neuroprotection or as a second tocolytic.

Recommended nifedipine dosage regime:

- **Initial** dose of 20mg
- Followed by three further doses of 20mg every 30 minutes if contractions continue.
- Maintenance dose is 20-40mg orally four hourly for 48 hours (no more than 160mg/24 hours).
    - Caution with doses > 60mg (refer to text)

The suggested initial nifedipine dose regime is an initial dose of 20mg, followed by three further doses of 20mg every 30 minutes if contractions continue. Maintenance dose is 20-40mg orally four hourly for 48 hours (no more than 160mg/24 hours). The dose may be titrated against tocolytic effect. However, doses over 60mg have a three to four fold increase in serious side effects (hypotension) and therefore should be used with caution (Khan et al, 2010).

Nifedipine side effects:

The following side effects have been reported in at least 1% of patients:

- Constipation, diarrhea, dizziness or lightheadedness, Flushing, headache, nausea.

- Uncommon side effects:

  - altered cardiac conduction, cutaneous vasodilation, drug-induced hepatitis, fluid retention, hypocalcaemia, hypoglycaemia, hypotension, tachycardia, altered uteroplacental blood flow, tachycardia.

4.5.3: Other Tocolytics:

Beta-agonists, such as ritodrine, reduce the sensitivity to calcium, and total intracellular calcium concentrations, thereby causing myometrial relaxation. Although beta-agonists have been licensed to treat PTL, they are rarely used today due to their adverse side effect profile - palpitations, tremor, tachycardia, pulmonary oedema, myocardial ischaemia, and hyperglycaemia (Anotayanonth et al, 2004; De Heus et al, 2009). Compared to placebo, beta-agonists have been shown to reduce the incidence of delivery within 48 hours (Anotayanonth et al, 2004) but they have not been proven to be superior to other tocolytics in preventing actual preterm birth (King et al, 2003; Crowther et al, 2002). The beta-2-receptor agonist Terbutaline is now not recommended for use in PTL due to these serious side effects (U.S. Food and Drug Administration, 2011). However, terbutaline is still used for emergency treatment of intrapartum uterine hyperstimulation to aid resuscitation of a fetal bradycardia.

Evidence is lacking to support the use of non-steroidal anti-inflammatories drugs (NSAIDs), such as indomethacin, to prevent preterm birth (King et al, 2005; Koren et al, 2006; Borna and Saeidi, 2007; McWhorter et al, 2004; Groom et al, 2005). Concerns exist regarding premature ductal closure, oligohydramnios, necrotizing enterocolitis, and intraventricular hemorrhage when NSAIDs are administered during the third trimester (Koren et al, 2006; Sood et al, 2011; Soraisham et al, 2010).

Transdermal nitroglycerine (a nitric oxide donor) has been suggested for use in PTL in one randomized trial, with similar efficacy to ritodrine. However limited data are available to determine side effect profile (Smith et al, 2007).

Magnesium sulphate theoretically has a role as a tocolytic due to inhibition of myometrial contractions, and its use has been widespread in North America for this indication. However there are little data demonstrating a significant reduction in preterm delivery or perinatal outcome (Doyle et al, 2009). Therefore magnesium sulphate is generally not used as a tocolytic in Europe. In contrast, there is now convincing evidence confirming pre-

delivery administration of magnesium sulphate before 32 weeks' gestation confers significant fetal neuroprotection. This has resulted in a reduced incidence and severity of cerebral palsy.

4.6 Observations recommended during tocolytic treatment:

- Hourly maternal vital sign monitoring, including temperature, pulse, blood pressure and respiratory rate for the first 4 hours.
- 4 hourly temperature, pulse and blood pressure during nifedipine treatment.
- Continuous CTG monitoring, while contractions continue.

4.7 Maintenance therapy/ Multiple Tocolytics

Maintenance therapy with atosiban (continuous subcutaneous infusion to 36 completed weeks' gestation) was shown to prolong pregnancy when compared to placebo in one study (Valenzuela et al, 2000). However overall there is insufficient evidence to justify maintenance tocolytic therapy following stabilization of an initial bout of PTL. Additionally, the principal goal of tocolytic therapy is to enable corticosteroid administration and transfer to a tertiary-level centre, rather than to continuously suppress contractions. Therefore maintenance tocolytic therapy is generally not recommended (De Heus et al, 2009).

Additionally, the use of multiple tocolytic agents is not recommended due to the risk of adverse effects, and also because of the increasing likelihood of a significant underlying pathologic cause of PTL (De Heus et al, 2009).

4.8 Tocolytics in Multiple pregnancy

There is no clear guidance on tocolytic agents to inhibit labour in multiple pregnancies, and they have not been shown to reduce the risk of preterm birth or improve neonatal outcomes (Cetrulo and Freeman, 1976; O'Leary, 1986; Yamasmit et al, 2005). The use of tocolytic agents in such cases has shown an increase in adverse events most notably pulmonary oedema (Ashworth et al, 1990).

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6. Implementation Strategy

- Distribution of guideline to all members of the Institute and to all maternity units.
- Implementation through HSE Obstetrics and Gynaecology programme local implementation boards.
- Distribution to other interested parties and professional bodies.

7. Key Performance Indicators for Consideration

- Number of women diagnosed with PTL/ TPTL.
- Number of women admitted to hospital who are observed only for PTL/ TPTL and where labour resolves.
- Overall obstetric and neonatal outcomes for women with a history of PTL/TPTL who were admitted to hospital during the course of their pregnancy.
- Number of women who were administered a Tocolytic agent for PTL.
- Choice of Tocolytic, duration of treatment and time of commencement of treatment from time of admission to hospital.
- Number of women in PTL who remained undelivered at 48 hours and 7 days after commencing treatment with tocolytics.
- Number of women receiving multiple tocolytics or maintenance therapy.
- Number of women who did not receive antenatal corticosteroids before 34 weeks gestation and delivered, as well as neonatal outcomes.
- Number of women in advancing PTL who did/did not receive magnesium sulphate in PTL before 32 weeks gestation and neonatal outcomes.
- Number of women who received 'rescue' steroids.
- Documented adverse effects during tocolytic treatment and number of women where tocolytics were discontinued before prescription was completed secondary to adverse effects.
- Involvement of Senior Obstetrician/ Consultant in decision regarding tocolytic treatment in PTL.

- Involvement of multidisciplinary team of neonatologists, obstetricians, labour ward staff, anaesthetists where applicable.
- Auditing hospital guideline on Tocolytic Treatment in Pregnancy.
- Regional auditing of interhospital transfer of patients whether due to need for transfer to tertiary centre with high risk neonatal services *or* need to transfer patients within high-risk centers due to lack of space, and any morbidity incurred as a result of transfer.
- Outcomes when *Atosiban* is used for PTL alongside *Magnesium Sulphate* for fetal neuroprotection when delivery is imminent (particularly if both are given in a 24 hour period).

8. Qualifying Statement

These guidelines have been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. Clinical material offered in this guideline does not replace or remove clinical judgment or the professional care and duty necessary for each pregnant woman. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion.
- Advising women of their choices and ensure informed consent is obtained.
- Meeting all legislative requirements and maintaining standards of professional conduct.
- Applying standard precautions and additional precautions, as necessary, when delivering care.
- Documenting all care in accordance with local and mandatory requirements.

Appendix 1 Table No 1: Tocolytic agents and side effect profile:

	Maternal Side Effects	**Fetal or Neonatal Adverse effects**	**Contraindications**
Calcium channel blockers	Dizziness, flushing, hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulphate; and elevation of hepatic transaminases	Altered Uteroplacental blood flow, tachycardia	Hypotension and pre-load-dependent cardiac lesions, eg aortic insuffuciency
Oxytocin Receptor antagonists (Atosiban)	Headache, dizziness, hot flushes, vomiting, tachycardia, hypotension, reaction at site of injection, hyperglycaemia, fever, insomnia, itching, rash, postpartum haemorrhage, serious allergic reactions		Chorioamnionitis/ sepsis, significant antepartum haemorrhage, such as placental abruption/ active vaginal bleeding; advanced cervical dilatation, abnormal CTG suggesting non-reassuring fetal status, placental insufficiency, pre-eclampsia/ eclampsia, lethal Congenital/chromosomal malformation, intrauterine fetal demise, maternal allergy to specific tocolytic agents, or where tocolytics are contraindicated with specific co-morbidities (e.g. beta-agonists should not be given in case of cardiac disease), gestational ages < 24 weeks or > 33+6 week.
Nonsteroidal anti-inflammatories	Nausea, oespophageal reflux, gastritis.	In utero constriction of ductus arteriosus, oligohydramnios, necrotizing enterocolitis in preterm newborns, and patent ductus arteriosus in newborn	Platelet dysfunction or bleeding disorder, hepatic dysfunction, ulcerative colitis, renal disease, asthma
Beta-adrenergic receptor agonists	Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary oedema, hypokalaemia and hyperglycaemia	Fetal tachycardia	Tachycardia-sensitive maternal cardiac disease and poorly controlled diabetes
Magnesium sulphate	Flushing, diaphoresis, nausea, loos of deep tendon reflexes, respiratory depression, cardiac arrest, suppresses heart rate, contractility and left ventricular systolic pressure when used with calcium channel blockers; and produces neuromuscular blockade when used with calcium channel blockers	Neonatal depression	Myasthenia Gravis

Table No.1 modified from Management of Preterm Labor. ACOG Practice Bulletin No.127. Obstet Gynecol. June 2012 (48)

Appendix 2:

Assess for Signs and Symptoms of Preterm Labour

- Lower abdominal cramping
- Pelvic pressure
- Lower back pain
- Vaginal bleeding or 'show'
- Regular uterine activity

Review history/ precipitating factors

- Medical
- Surgical
- Obstetric
- Fetal abnormality
- Bleeding
- Infection
- Multiple pregnancy
- Membrane rupture

Current pregnancy

- Confirm gestation, singleton etc
- Ultrasound- EFW, BPP, Amniotic fluid, position of placenta, engagement of presenting part where appropriate
- Vaginal exam to assess cervical status

Physical Examination

- Vital signs (temp, HR, BP)
- Abdominal examination (for placental abruption/ chorioamnionitis
- MSU
- FBC,
- CTG

Investigations

- Sterile speculum examination
- Outrule PPROM
- HVS if indicated Low vaginal/ anorectal GBS swab

At very early gestations < 24 weeks discussion with parents regarding expected

Advancing Labour

- Corticosteroids
- Inform senior Obstetrician/ Labour ward/ NICU
- Magnesium sulphate bolus
- If cephalic presentation aim for vaginal delivery with caesarean for normal obstetric indications
- Continuous CTG
- Instrumental delivery only for standard obstetric indications
- Experienced paediatrician in attendance

Actual PTL diagnosed and at risk of delivery within 7 days, and no contraindication to Tocolysis:

- Consider transfer to tertiary centre (inform NICU, bed manager) and liaise with senior obstetrician
- Administer corticosteroids
- Atosiban or nifedipine (see text for dose regimes) can be administered on prenatal ward

TPTL

- Offer admission
- Observe for 24 hours
- Corticosteroids at clinician discretion
- Contracting but irregularly- reassess VE in 2 hours, if no change and settling consider discharge and follow up ANC x 1/52