Preterm Labor

This document describes guidelines for the initial evaluation, diagnosis, and management of a patient with preterm labor with a focus on the use of tocolytic medications.

I. Preface

Definition
Preterm labor will be defined as regular uterine contraction, every 5-10 minutes or 6-10 in one hour before 37 weeks' associated with:

1. Progressive cervical effacement of dilatation
2. >2cm dilation or >80% effacement.

General
Preterm labor resulting in preterm delivery continues to be the leading cause of perinatal morbidity and mortality. Occult infection has been recognized as one of the major causes of preterm labor and of failed tocolysis. Studies suggest that inflammatory processes may account for perhaps 20-30% of cases preterm delivery.

Requirements for Consideration of Labor Suppression

1. Lack of evidence supporting fetal maturity with a live fetus.
2. Absence of maternal or fetal conditions dictating delivery.
3. Generally should not be attempted if cervix is 6cm or more dilated. However tocolysis may still be considered to allow time for corticosteroid therapy. Betamethasone 12.5 mg may still be considered to allow time for corticosteroid therapy (See applicable protocol)
4. PPROM warrants special considerations (See applicable protocol)

Gestational age considerations

1. If the patient is < 34 0/7 weeks’ gestation and demonstrated cervical change, she is a candidate for tocolysis.
2. If the patient has premature uterine contractions but does not experience cervical change, the contractions may be treated with judicious hydration and sedation and observed over several hours for cervical change. On transvaginal ultrasound, a cervical length < 25 mm (<10%ile) increases the likelihood of preterm delivery. Such data may help triage patients.
3. If the patient is ≥ 34 0/7 weeks with reliable dates, allow delivery.
4. If the patient is 22-34 weeks gestation, perform an ultrasound to rule out obvious fetal anomalies, confirm EGA, and establish EFW (see below)

Decisions regarding tocolysis necessitate discussion with the patient regarding risk, benefit and efficacy
II. Diagnosis

1. Confirm the diagnosis of preterm labor (PTL)
   a. Document regular contractions, q5-10 minutes or 6-10 in 1 hour associated with either:
      i. Progressive cervical effacement or dilatation
      ii. $\geq 2$ cm dilation or $\geq 80\%$ effacement
   b. Verify estimated gestational age (EGA) <34 wks (<32 wks if PPROM). Consider amniocentesis for fetal lung maturity (FLM) testing if EGA $\approx 34$ wks with late or unsure gestational dating.
      i. Caution should be taken, with consideration to avoid tocolysis or discontinue therapy following transport when corticosteroids for FLM are not indicated (for example, <23 wks EGA [Level I evidence]).

III. Evaluation

1. Rule-out evidence of chorioamnionitis
   a. Consider amniocentesis for Gram stain, culture, cell counts & glucose when clinically indicated.

2. Confirm absence of maternal or fetal conditions dictating delivery
   a. Evaluate fetal well-being
      i. NST or BPP as indicated
      □ Caution in the setting of vaginal bleeding or concern for abruption

3. Ultrasound
   a. Document: fetal number, presentation, weight, and amniotic fluid index
   b. Estimate gestational age/weight
   c. Rule-out major fetal anomalies
   d. Except in emergent situations, should be completed in triage
      i. Ultrasound images should be reviewed by a PGY-3, 4, or MFM fellow or attending
   e. If the patient has had no prior ultrasounds, a senior resident, fellow, or attending must be present for the ultrasound or the scan should be repeated on the patient’s arrival to the Labor & Delivery floor.
   f. Outside ultrasounds that are not available at the time of admission should be obtained.

4. Perform a sterile speculum exam
   a. Evaluate for occult PPROM
   b. Obtain swabs for GBS, GC (optional), and chlamydia (optional)

5. Labs
   a. CBC
b. Clean catch or catheter UA with culture
c. Rapid HIV as indicated per protocol
d. Other labs as indicated

IV. Management

1. Admit to labor and delivery
   a. Tocolytics may be initiated in triage if concern for rapid progression of PTL
      i. Transfer to labor and delivery as soon as practicable after initiation of tocolytics
   b. External fetal monitoring and tocometry during tocolysis as per protocol

2. Administer first dose of corticosteroids for FLM acceleration [Level I evidence]¹,²
   a. Betamethasone 12.5mg IM q24h x 2 doses is the preferred agent
   b. Dexamethasone 6mg IM q12h x 4 doses is an alternative regimen
      (See applicable corticosteroid protocol)

3. Administer antimicrobial agents [Level A recommendation from ACOG]²
   a. PTL – antibiotics for GBS prophylaxis per protocol
   b. PPROM – antibiotics for latency per protocol
   c. Antibiotics or antifungals as indicated for suspected cervicitis/vaginitis

4. Consider tocolysis
   a. First-line agent = Nifedipine (Procardia).
      Although no tocolytic agent has been shown to be definitively effective or superior [Level A recommendation from ACOG]², Nifedipine is the tocolytic drug with the most benign side-effect profile and data most suggestive of neonatal benefit [Level I evidence].³,⁴
      i. Method of action: Calcium channel blocker
      ii. Regimen: Oral (not sublingual) loading dose of 10 mg (immediate release) Q 10 mins (for a total loading dose of 30 mg) then standard starting dose of 20 mg q6 (beginning 6 hours after loading dose).
         1. Titration range- Dose may be adjusted with administration of between 10-20 mg PO q 4-6 hours
         2. Maximum daily dose 160 mg/day
      iii. Pharmacokinetics: onset of effect in ~20 minutes, peak plasma concentrations reached between 30 and 60 minutes
      iv. Contraindications
         • Patients with known or suspected cardiac conduction disorders (including Wolf Parkinson White Syndrome, etc)
         • Caution with hepatic or renal disease
         • Maternal hypotension (<90/50)
      v. Modest decrease in diastolic blood pressure expected

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• ~20 minutes after second oral dose
• generally transient and not clinically significant
• often accompanied by a mild unsustained increase in maternal heart rate
• little to no effect on uterine perfusion

vi. Side-effects:
• Common:
  • Flushing (96%) - transient
  • Headache (38%) - Often resolves after initial 1-2 doses
  • Nausea - uncommon
• Less common:
  • Transient lightheadedness
  • Palpitations
  • Chest pain
  • Nasal congestion
  • Heartburn
• Mild increase in serum glucose (consistently <120 mg/dL)

Comment:
_Nifedipine is a dihydropyridine calcium channel blocking agent. Cardiac conduction effects are generally minimal from the use of dihydropyridine calcium channel blocking agents. In certain circumstances, at the direction of MFM recommendations Nifedipine may be used in combination with magnesium sulfate._

_Non-dihydropyridine calcium channel blocking agents (eg., verapamil) are generally not used in obstetrics for tocolysis and should never be used in combination with other calcium channel blocking medications (magnesium sulfate). In our unit for the purpose of tocolysis, nifedipine will be the calcium channel blocking agent that is used._

b. Second line tocolytic agent: If EGA<34 0/7 weeks and there is evidence of persistent cervical change (dilatation or effacement) while on Nifedipine then consider Indomethacin as the second-line agent at this EGA [Level C recommendation; some Level 1 evidence]5,7

i. Method of action: Prostaglandin synthetase inhibitor
ii. Regimen: Oral loading dose of 50mg followed by 25 mg PO q6h (dosing modification from this regimen per specific MFM recommendation).
iii. Pharmacokinetics: onset of effect in 30 minutes; peak blood levels expected 1-2h after loading dose; duration of action 4-6h.
iv. Document a normal amniotic fluid volume (AFV) prior to administration
v. Contraindications to the use of Indomethacin
  • Peptic ulcer disease
• Uncontrolled hypertension
• Bleeding diatheses
• Renal disease
• Hepatic dysfunction
• Aspirin-induced reactive airway disease

vi. Prolonged bleeding time has been documented (PT/PTT not affected)

vii. Other side effects rare in healthy adults
• I/O’s should be monitored as fluid retention and decreased urine output are possible
• Could exacerbate electrolyte imbalance (↑ K+, ↓ Na+)

viii. Potential fetal side-effects:
• Reduction in AFV
  ▪ Reduction (not oligohydramnios) as been documented as early as 4h after first dose
  ▪ Repeat AFV assessment not required as therapy will be limited to 48h and AFV reduction is limited & reversible with short term therapy

• Constriction of ductus arteriosus
  ▪ Of minimal concern as therapy will be limited to <34 0/7 wks EGA and ≤48h duration

ix. Indomethacin is typically not a second line tocolytic in patients with Twin Twin Transfusion Syndrome.
x. Although allowable to give second line tocolysis in gestations between 32 0/7 and 33 6/7 weeks’ gestation, benefit less clear than in those gestations of less than 32 0/7 weeks’. Second line tocolysis should therefore be individualized.

d. Magnesium sulfate may be considered if a patient is transferred from an outside hospital on a magnesium sulfate infusion and is stable or if specific clinical consideration warrants its use- gestational age considerations as with nifedipine and indomethacin
  i. Loading dose is 6g given over 30 minutes (not to be repeated if a patient is already on magnesium sulfate from a transferring institution)
  ii. Infusion is to be run by controlled infusion pump “piggy back” into primary IV line.

e. Maintenance dose: 3 g IV per hour starting dose (range 2-4 g IV / hour)
  i. Clinical examination and serum Mg levels can be used to monitor dose effect.
  ii. Serum levels of 5-8 mg/dL are thought to be therapeutic
  iii. 6g bolus followed by 3-4 g/h have been shown to give serum levels of 6.5-7.5 mg/dL
  iv. Serum magnesium levels are to be checked 2 hours after the loading dose and then every 8 hours while on the continuous infusion.
v. Patients transferred on magnesium should have serum magnesium levels drawn on arrival and then every 8 hours while on the continuous infusion.
f. Discontinue magnesium sulfate infusion if…
   i. It is discovered the patient has contraindications to the therapy
      • Absolute – myasthenia gravis and heart block
      • Relative – underlying renal disease and recent MI
   ii. There is evidence of maternal magnesium toxicity
      • STOP magnesium infusion and check serum magnesium levels if toxicity suspected
      • urgent physician notification for magnesium level over 8 mg/dL
      • STOP magnesium infusion for magnesium level > 10 mg/dL and notify physician
   iii. Interpretation of NST and BPP may be altered due to the increase in maternal magnesium.
   iv. There is evidence of moderate-severe maternal renal impairment
      • Caution when urine output <40cc/h or serum Cr>0.8 mg/dL
      • Loading dose may maintain therapeutic level for extended period in patients with renal insufficiency

g. Discontinue magnesium sulfate infusion after 48h except in rare circumstances. Prolonged tocolysis (>48 hours) has not been shown to improve maternal/fetal outcome and may provide increase risk for adverse drug effects [Level A recommendation from ACOG].
   i. “Weaning” or tapering the dose is not necessary. [Level I evidence]
   ii. Magnesium should be stopped, not weaned when discontinued.

h. Maternal monitoring while on magnesium sulfate
   i. Strict bedrest
   ii. Strict I/O’s ± Foley catheter
   iii. Monitor closely for evidence of toxicity
      • Document vitals, oxygen saturation, symptoms, alertness, DTRs, pulmonary exam

i. Emergency therapy for severe magnesium toxicity: administer one ampule Ca2+ gluconate 1g (10mL of a 10% solution) IV over 3 minutes for reversal.

5. Long-Term maintenance tocolysis:
   a. Maintenance tocolysis is not recommended as general practice [Level A recommendation from ACOG]. Maintenance tocolysis after acute therapy has not been shown to be effective in reducing neonatal morbidity or mortality.

   b. Prolonged tocolytic therapy, whether by oral, subcutaneous or intravenous route, has not been shown to be effective [Level I-III evidence depending on tocolytic agent studied]. Furthermore, prolonged used of any tocolytic drug may potentially increase maternal-fetal risk without offering clear benefit.
c. Prophylactic therapy with tocolytic drugs in patients at high risk for preterm delivery, is not recommended since it has not been proven to be effective in improving neonatal outcome, and prolonged therapy may increase maternal-fetal risk [Level I evidence].

6. Combining tocolytic drugs:
   a. Combination tocolytic therapy is generally not recommended as combining tocolytic drugs may increase maternal morbidity and has not been proven to improve efficacy. However, there are special circumstances under which combined tocolytics can be considered. [Level III evidence].

   Special circumstances (polyhydramnios, Twin to twin transfusion syndrome, etc) may warrant combination tocolysis for salvage therapy. If combination tocolysis is warranted MFM faculty/fellow rationale and recommendations are required to be specifically placed outlining use of multiple agents and why they are indicated.

7. Tocolysis in patients with preterm contractions without cervical change:
   a. No evidence exists to support the use of tocolytic drugs in patients with preterm contractions but no cervical change [Level I & II-2 evidence].

V. References:


