These guidelines are informational only. They are not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient's needs on an individual basis. Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

BACKGROUND

1. Premature labor can be defined as regular uterine contractions with associated cervical change that occur before 37 weeks gestation.
2. Preterm birth is the leading cause of neonatal mortality in the United States and preterm labor precedes 40-50% of preterm births. Preterm births are responsible for three fourths of neonatal mortality and half of long term neurologic impairments in children. Gestational age is inversely proportional to the risk of neonatal morbidity and mortality.
3. Approximately 467,000 live births annually (11.5% of all live births) occur before term in the United States.
4. Preterm delivery will not occur in 80% of women with presumptive preterm labor.
5. The causes of preterm labor are not well understood.
6. Only ultrasonography to determine cervical length and fetal fibronectin testing have shown to be helpful in identifying patients at risk for progressing to preterm birth. Both have good negative predictive value alone or in combination for determining which patients do not need tocolysis.
7. Pharmacologic treatment (tocolytic therapy) may prolong gestation for 2-7 days. The goal of tocolytic therapy is to allow for administration of antenatal corticosteroids to improve fetal maturity and or consideration for transport to a tertiary facility.
8. There is no clear “first line” tocolytic agent. Clinical circumstances and physician preferences should dictate treatment.
9. Maintenance tocolytic therapy and repeated acute tocolysis do not improve perinatal outcome. Neither should be undertaken as a general practice.
10. Combining tocolytic drugs potentially increases maternal morbidity and should be used with caution.
11. Antibiotics used to prolong pregnancy and reduce neonatal morbidities in women with preterm labor and intact membranes do not appear to prolong gestation or improve short term neonatal benefits and may increase neonatal morbidity. Antibiotic therapy should be reserved for group B streptococcal prophylaxis in women with preterm labor with intact membranes.
12. Non-pharmacologic or preventative treatments such as bed rest, abstention from intercourse and orgasm, and hydration do not appear to improve the rate of preterm birth and should not be routinely recommended.
13. Amniocentesis to assess fetal lung maturity and intra-amniotic infection may be useful in select cases.
14. A recent meta-analysis pooling the results of the clinical trials of magnesium sulfate for neuroprotection suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Currently no single ideal protocol has been established. Recommended guidelines are based on currently available published treatment trials.
15. Premature rupture of the membranes (PROM) is defined as rupture of membranes prior to the onset of labor. Preterm PROM refers to rupture of the membranes before 37 weeks. The incidence of preterm PROM is reported to be 2.0 to 3.5%. 30-40% of preterm neonates are born to women with preterm PROM.
16. Use of prophylactic tocolysis (tocolysis before preterm uterine contractions have started) after preterm PROM has been shown to prolong latency in the short term. Therapeutic tocolysis (starting tocolysis after contractions have ensued) has not been shown to prolong latency. Retrospective studies have not demonstrated prolonged latency with aggressive tocolysis. The use of tocolysis in PPROM remains controversial.
17. The National Institutes of Health Consensus Development Panel has recommended a single course of antenatal corticosteroids for women with PROM before 32 weeks of gestation in the absence of intra-amniotic
18. **Prophylactic antibiotics appear to reduce the incidence of RDS, perinatal morbidity and mortality.** Its combined use with antenatal steroids does not appear to increase the incidence of perinatal infection. Based on the best available data, a 7-day course of parenteral and oral therapy with ampicillin or amoxicillin and erythromycin is recommended during expectant management of preterm PROM remote from term to prolong pregnancy and to reduce infectious and gestational age-dependent neonatal morbidity.

19. **The use of latency/prophylactic antibiotics** for women with PROM is different from prophylaxis against vertical transmission for GBS. Women who are known carriers of GBS should receive intrapartum prophylaxis to prevent vertical transmission regardless of earlier treatments.

20. **Use of a rescue dose of corticosteroids** if the first dosing regimen was given more than two weeks before the patient has recurrent labor and if the patient is less than 32 weeks on the second admit.

21. Evidence suggests a potential benefit to delaying delivery of a stable preterm PROM patient to between 34 and 35 weeks gestation. This is associated with a decrease in neonatal morbidity and a shorter nursery stay. This is associated with a decrease in neonatal morbidity and a shorter nursery stay. This may outweigh potential risks due to perinatal/neonatal infections. Most studies show that the benefit does not outweigh the risks after 35 weeks.

**RECOMMENDATION**

I. **General Principles of Care**

A. Although labor in its advanced stage may be readily apparent, early signs and symptoms of preterm labor are frequently so subtle and insidious that they are unrecognized or even ignored by the patient or health care provider.

B. The ability to prevent preterm deliveries is largely a function of early recognition and timely intervention of preterm labor in the current pregnancy as well as offering women with a history of prior preterm delivery the opportunity to take 17 alpha-hydroxyprogesterone caproate in subsequent pregnancies.

C. Pregnant women need to be educated about the early detection of preterm labor, including early symptoms, the identification and timing of uterine contractions, and the timely notification of health care workers. Early symptoms of preterm labor include:

   1. Regular uterine tightening with or without pain
   2. Low backache with pressure or pain, intermittent or constant
   3. Menstrual-like cramps felt in the lower abdomen or in the upper thighs
   4. Pelvic pressure which feels like the baby pushing down
   5. Abdominal cramping with or without diarrhea
   6. Change in the character of vaginal discharge, especially mucoid, watery or blood-tinged
   7. Possible rupture of the membranes
   8. Vaginal spotting or bleeding

D. The clinician must attempt to make an early accurate diagnosis of preterm labor, without overzealous treatment of patients not truly in labor. In patients with threatened preterm labor, contractions may stop with rest and hydration.

E. **Criteria for Diagnosis of Preterm Labor**

   1. Gestational age between 20 and 37 weeks and
   2. Documented regular uterine contractions at least every 10 minutes and one of the following:
      a. Documented cervical change over a period of observation
      b. Positive fetal fibronectin
      c. Initial cervical dilation greater than 2 cm
      d. Initial cervical effacement greater than or equal to 80%
      e. Endovaginal cervical length measurement of 2.5 cm or less
II. Initial Labor and Delivery Assessment and Management for Preterm Labor with Intact Membranes

A. Apply the external fetal and uterine contraction monitor
   1. Evaluate frequency and duration of contractions
   2. Palpate fundus to assess strength of contractions
   3. Evaluate fetal heart rate for well-being

B. Obtain maternal vital signs. Record baseline temperature, pulse, respiration and blood pressure.

C. Empty bladder. Obtain clean catch urinalysis and culture. Inquire regarding signs/symptoms of urinary tract infection. Obtain a straight cath urine if: 1) Suspicion of UTI/Pyelonephritis or 2) Preterm Premature Rupture of Membranes (PPROM).

D. Review prenatal records. Obtain history of current problem and inquire regarding signs or symptoms of preterm labor.

E. Ascertain gestational age, using best obstetrical clinical estimate.

F. Baseline cervical exam done by Provider.
   1. Speculum exam:
      a. if spontaneous ruptured membranes is possible
      b. if vaginal bleeding is to be evaluated
      c. if cervical/vaginal specimens are needed
         a. GC
         b. Chlamydia
         c. Group B strep
   2. Fetal fibronectin (see protocol)
   3. Gentle cervical exam: (avoid if PROM and not in labor) to assess dilation, effacement (may be recorded as length), consistency, and station of presenting part
   4. Check presenting part by vaginal exam, Leopold’s or ultrasound.
   5. Endovaginal cervical length study

G. If criteria are met for the diagnosis of preterm labor (see above), evaluate for immediate institution of tocolytic therapy. If initial cervical exam is greater than or equal to 4 cm, successful inhibition of preterm labor is less likely and preparation for potential preterm delivery is recommended.

H. Evaluate maternal hydration status (dehydration may be associated with increased uterine activity).
   1. Offer clear liquids if oral hydration is indicated
   2. Establish intravenous fluid hydration; 500 ml D5 LR or D5 ½ NS over 30 minutes, then 125 - 250 ml/hour for 2 hours
   3. Record intake and output

J. If criteria for the diagnosis of preterm labor are not met at the initial exam, subsequent cervical exams at 1 - 2 hour intervals may be necessary to evaluate for cervical change. The same examiner is more likely to accurately detect subtle cervical changes.
   1. Reassess contraction strength and frequency
   2. Reassess patient symptoms
   3. If serial cervical exams document cervical change, then criteria for preterm labor (see above) are met, and the patient is evaluated for immediate institution of tocolytic therapy

K. Fetal assessment (as indicated)
   1. Fetal heart rate evaluation to assess well being
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2. Sonographic evaluation for
   a. fetal presentation
   b. estimated gestational age
   c. estimated fetal weight
   d. amniotic fluid volume
   e. anomaly screen
   f. cervical length assessment

L. Amniocentesis as clinically indicated
   1. Lung maturity profile
   2. Additional Tests
      a. Gram Stain (Suggestive of intra-amniotic infection presence of any bacteria or > 6 WBC per HPF).
      b. WBC (Suggestive of intra-amniotic infection > 50 cells/uL)/
      c. Amniotic Fluid Glucose (Suggestive of intra-amniotic infection if < 14 mg/dL).
      d. Cultures: Anaerobic, Aerobic and mycoplasma.
      e. Instillation of indigo carmine dye (1ml in 9 ml of sterile normal saline) followed by the observation for passage of blue fluid from the vagina within 30 minutes of the amniocentesis

M. Antenatal corticosteroids
   1. Indications
      a. Gestational age 24-34 weeks. (consider initiating at 23 weeks after consultation with MFM and Neonatology)
      b. Preterm birth is anticipated before 34 weeks gestation
      c. No clinical evidence of infection
   2. Corticosteroid dosage
      a. Betamethasone 12 mg IM and repeat in 24 hours x 1 dose
      b. Dexamethasone 6 mg. IM every 12 hours x 4 doses
      c. Single treatment course
      d. Routine repeat courses are not recommended

N. Antibiotic therapy for neonatal Group B strep sepsis prophylaxis until cultures return. (See Regional Protocol)

O. Communication with the NICU Team
   1. A member of the NICU team should have an opportunity to talk to the mother and appropriate family members.
   2. Consultation with the neonatologist is essential in assisting in the prediction of potential neonatal viability. This will influence decisions about method of delivery and the extent of resuscitation of the neonate.

III. Initial Labor and Delivery Assessment and Management for Preterm Labor with Preterm Premature Rupture of Membranes

A. Apply the external fetal and uterine contraction monitor
   1. Evaluate frequency and duration of contractions
   2. Palpate fundus to assess strength of contractions
   3. Evaluate fetal heart rate for well-being

B. Obtain maternal vital signs. Record baseline temperature, pulse, respiration and blood pressure.

C. Empty bladder. Obtain clean catch urinalysis and culture. Inquire regarding signs/symptoms of urinary tract infection. Obtain a straight Cath for PPROM.

D. Review prenatal chart. Obtain history of current problem and inquire regarding signs or symptoms of preterm labor.
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E. Ascertain gestational age, using best obstetrical clinical estimate.

F. Sterile speculum examination
   1. Confirm rupture of membranes.
      a. Nitrazine paper
         • Turns blue at pH of 6.0-6.5
         • Vaginal secretions usually have a pH of 4.5-6.0
         • Amniotic fluid pH is 7.1-7.3
      b. Gross pooling of amniotic fluid in the vaginal vault.
      c. Presence of arborization (ferning) on microscopic exam of air dried amniotic fluid
      d. Transabdominal instillation of indigo carmine dye (1ml in 9 ml of sterile normal saline) followed by the observation for passage of blue fluid from the vagina within 30 minutes of the amniocentesis.
   2. Collect vaginal cultures (Neisseria gonorrhea, Chlamydia trachomatis and group B streptococcus).
   3. Note that fetal fibronectin is not valid with rupture of membranes.
   4. Vaginal pool or amniocentesis for fetal lung maturity (fetal lung maturity profile, gram stain, cell count, glucose if an amniocentesis is done) if gestational age greater than 32-34 weeks.
   5. Digital cervical examinations should not be performed in patients with preterm PROM who are not in labor and in whom immediate induction of labor is not planned.

G. Ultrasound for presentation, estimated fetal weight and AFI.

H. Additional Labs: CBC

I. Amniocentesis as clinically indicated
   1. This may be particularly important if maternal fever is present and the etiology is obscure
   2. Fetal lung maturity profile
   3. Gram stain (Suggestive of intra-amniotic infection presence of any bacteria or > 6 WBC per HPF).
   4. Glucose (Suggestive of intra-amniotic infection < 20 mg/dL).
   5. WBC count (Suggestive of intra-amniotic infection > 30 cells/µL).
   6. Culture Anaerobic, Aerobic and mycoplasma

J. Antibiotic Prophylaxis
   1. First 48 hours
      a. Ampicillin 2 grams IV every 6 hours
      b. Azithromycin 1g PO
   2. Next 5 days
      a. Amoxicillin 250 mg every 8 hours
   3. GBS positive patients
      a. First 48 hours of treatment same as above.
      b. Ampicillin 500 mg every 6 hours for 5 days instead of oral Amoxicillin.
      c. Treat with intrapartum Penicillin per GBS protocol when in labor.

K. Antenatal Steroids
   1. Recommended if:
      a. Gestational age between 24 and 34 weeks. (consider initiating at 23 weeks after consultation with MFM and Neonatology)
      b. No clinical evidence of infection.
   2. Steroid type and dose:
      a. Betamethasone 12 mg IM and repeat in 24 hours x 1 dose or
      b. Dexamethasone 6 mg IM every 12 hours x 4 doses
      c. “Rescue therapy” should not be routinely used.

L. Communication with the Neonatal Intensive Care Unit Team
   1. If time permits, a member of the Neonatal team should have an opportunity to talk to the mother and appropriate family members.
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2. Consultation with the Neonatologist is essential in assisting in the prediction of potential neonatal outcomes. This will influence decisions about method of delivery and the extent of resuscitation of the neonate

M. Suggest expectant management if
   1. Gestational age less than 35 weeks.
   2. No evidence of labor.
   3. No evidence of chorioamnionitis.
   4. No evidence of fetal compromise on fetal monitor.

N. Tocolytic therapy
   1. Tocolytic therapy in patients with preterm rupture of membranes is controversial.
   2. Tocolytic therapy can be considered on an individual (case by case) basis in the first 24 to 48 hours to allow time for the administration of antenatal steroids.
   3. Tocolytic therapy is not recommended if the duration of rupture of membranes is greater than 48 hours and should be discontinued after 48 hours.

O. Suggested antepartum management.
   1. Daily non-stress test
   2. Consider weekly AFI check
   3. Delivery if any evidence of maternal or fetal infection, abnormal fetal monitoring or recurrent preterm labor.
   4. Induction of labor at 35 weeks gestation or when fetal lung maturity is documented.

IV  TOCOLYTICS FOR PRETERM LABOR

A. Magnesium sulfate
   1. Dosage and administration
      a. 2-6 gram bolus over 20 minutes
      b. Continuous intravenous infusion 2-3 grams per hour.
   2. Contraindications
      a. Myasthenia gravis
   3. Maternal side effects
      a. Flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema, cardiac arrest.
   4. Fetal and neonatal side effects
      a. Lethargy, hypotonia, respiratory depression, demineralization of bone with prolonged use.

B. Nifedipine (Calcium channel blockers)
   1. Dosage and administration
      a. 10 mg loading dose orally every 20 minutes. Maximum loading dose 30 mg.
      b. 10-20 mg every 4-6 hours
      c. Hold for blood pressure less than 90/50 mm Hg
   2. Contraindications
      a. Cardiac disease
      b. Use with caution with renal disease
      c. Maternal hypotension (blood pressure less than 90/50 mm Hg)
      d. Concomitant use with magnesium sulfate
   3. Maternal side effects
      a. Flushing, headache, dizziness, nausea, transient hypotension
   4. Fetal and neonatal side effects
      a. None noted as yet

C. Indomethacin (Prostaglandin synthetase inhibitors)
   1. Dosage and administration
      a. 50 mg loading dose rectally or 50 to 100 mg orally
      b. 25 to 50 mg orally every 6 hours for 48 hours.
   2. Contraindications
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a. Gestational age 32 weeks or greater
b. Significant renal or hepatic impairment
c. Active peptic ulcer disease
d. Coagulation disorders or thrombocytopenia
e. Known hypersensitivity (including acute asthmatic attacks, urticaria, etc) to indomethacin, aspirin, or other NSAIDs
f. Rectal suppositories are contraindicated in patients with rectal bleeding

3. Maternal side effects
   a. Nausea, heartburn

4. Fetal and neonatal side effects
   a. Constriction of the ductus arteriosus, pulmonary hypotension, reversible decrease in renal function with oligohydramnios, intraventricular hemorrhage, hyperbilirubinemia, necrotizing enterocolitis

V MAGNESIUM SULFATE FOR NEUROPROTECTION

A. Magnesium Sulfate for Neuroprotection Protocol
   1. Gestational age 24-32 weeks. (consider initiating at 23 weeks after consultation with MFM and Neonatology)
   2. Recurrent preterm labor or anticipated preterm delivery within 24 hours.
   3. Dosage
      a. 4 to 6 gram intravenous load.
      b. 1 to 2 gram per hour intravenous continuous infusion maintenance.
      c. Discontinue treatment after delivery of infant or duration of treatment up to 24 hours (which ever occurs first).
      d. Re-treatment if delivery occurs after 24 hours is currently not recommended.
      e. Contraindication: Myasthenia gravis.

VI REFERENCES

