10/30/16njm

ANMC WOMEN'S HEALTH SERVICE
GUIDELINES FOR THE MANAGEMENT
OF PRETERM LABOR

Goals:

Idiopathic preterm labor cannot be inhibited for prolonged periods of time. Therefore, the goals when treating this condition are to:

- Delay delivery so that corticosteroids can be administered.
- Allow safe transport of the gravida, if indicated, to a facility that can provide an appropriate level of neonatal care if the patient delivers preterm.
- Prolong pregnancy when there are underlying, self-limited causes of labor, such as pyelonephritis or abdominal surgery, which are unlikely to cause recurrent preterm labor.

Definitions:

Preterm Labor - regular uterine contraction after 20 weeks or before 37 weeks GA, which occur regularly, leading to progressive cervical change.

Associations with preterm birth:

1. Preterm premature rupture of membranes (see below)
2. Chorioamnionitis
3. Fetal anomalies
4. History of prior preterm labor
5. Multiple gestation
6. Polyhydraminos
7. Intrauterine fetal demise
8. Cervical insufficiency
9. Uterine anomalies
10. Placenta previa or abruptio placentae
11. Retained IUD
12. Serious maternal disease (e.g., preeclampsia)
13. Cervical conization or L.E.E.P.
14. Idiopathic

Preterm birth due to:

- PROM 35% of the time
- Maternal fetal complications 35%
- Idiopathic preterm labor 30%

Risks of recurrent preterm birth

First Birth	Second Birth	Next Birth Preterm
term	----------	5%
preterm	----------	15%
term	preterm	24%
preterm	preterm	32%

Routine Antibiotics, e. g., not just for Beta Strep prophylaxis
A Cochrane review concluded that antibiotics CANNOT be recommended in the routine management of women in preterm labor with intact membranes. A subgroup of women who have subclinical intrauterine infection theoretically might benefit from treatment with antibiotics, but there is no means for identifying these women at this time. It is also possible that the infectious process may be too advanced by the time preterm labor is clinically apparent for treatment to be effective.
A subsequent RCT confirmed the meta-analysis described above and affirmed the recommendation against routine antibiotic administration to women in preterm labor without evidence of infection.

CONTRAINDICATIONS TO TOCOLYSIS — The general contraindications to labor inhibition are:

- Intrauterine fetal demise
- Lethal fetal anomaly
- Nonreassuring fetal assessment
- Severe intrauterine growth restriction
- Chorioamnionitis
- Maternal hemorrhage with hemodynamic instability
- Severe preeclampsia or eclampsia

Known or suspected fetal maturity is not necessarily a contraindication to tocolysis as there are nonpulmonary morbidities associated with preterm birth. For example, a 30 week fetus with a mature amniotic fluid test is still at risk for intraventricular hemorrhage, sepsis, hyperbilirubinemia, and other morbidities unrelated to hyaline membrane disease. These fetuses could potentially benefit from prolongation of pregnancy. Inhibition of preterm labor is less effective when cervical dilatation is advanced (greater than 3 cm). Tocolysis can also be considered in these cases, especially when the goal is to administer antenatal corticosteroids or safely transport the gravida to a tertiary care center.

Other Background
Betamimetics help to delay delivery for women transferred to tertiary care or completed a course of antenatal corticosteroids, but are not recommended as a first line tocolytic or for long term therapy.

The evidence from this new review supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. A single course of antenatal corticosteroids should be considered routine for preterm delivery with few exceptions.

Numerous large clinical studies have evaluated the evidence regarding magnesium sulfate, neuroprotection, and preterm births. None of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants.

Management:

1. History of Preterm Labor with preterm delivery
   a. preconceptual counseling to eliminate risk factors, e.g., stop tobacco, alcohol, drugs, space pregnancies, good nutrition, normalize hypertension, stabilize maternal medical conditions, anticipate need for increased pregnancy surveillance and prophylactic rest.
   b. early pregnancy care
   c. excellent dating by exam and early ultrasound
   d. obtain cervical length 18-24 wks+
   e. urine culture x1
   f. preterm labor education by qualified personnel by 20 to 23 weeks GA.
   g. intensive monitoring for signs and symptoms of recurrent preterm labor and/or asymptomatic cervical change
      signs & symptoms:
         *increased vaginal discharge
         *blood tinged mucus
         *low backache
         *pelvic pressure
         *menstrual - like cramps
         *intestinal cramping, with or without diarrhea
         *"not feeling right"
         *precocious cervical dilations (1 cm or more)
   j. If cervical changes, or transvaginal ultrasound cervical length <2.5 cm, or fibronectin fFN positive- remain in urban area for routine prenatal care

      2) If local resources do not permit, consider counseling the patient to remain in urban area regardless of cervical findings. Time of patient remaining in urban area should be based on prior time of preterm birth.
   k. See Progesterone for the Prevention of Recurrent Preterm Birth guideline

+ If transabdominal cervical length is < 2.5, then obtain transvaginal cervical length

2. History of preterm labor with Term Delivery- Same as 1.
3. History of preterm labor due to prior maternal or fetal Complications
   a. Reassess risk of recurrence
      -if prior preterm birth associated with nonrecurring condition, i.e. twins, preterm birth risk probably same as "normal" singleton pregnancy.
   b. Liberally consult OB-GYN to determine risk of recurrent preterm labor and management.

4. **Current preterm labor**

Step One
   a. Review pregnancy dating
   b. Obtain cervico-vaginal swab for fFN <u>before</u> you perform cervical exam (a negative fFN has a 99% negative predictive value [NPV] for not delivering in the next 7-10 days, but a positive fFN only has a positive predictive value [PPV] of 13%).

c. Obtain transvaginal cervical length (TVCL) if possible
(a TVCL of >2 cm has a NPV for not delivering in the next 7-10 days of 96%, but a TVCL <2 cm has a PPV of only 18%).
d. Obtain rectovaginal swab for group B strep (GBS)
(repeat screening for gonorrhea and chlamydia not necessary if negative earlier in pregnancy).

Step Two

a. Rule out maternal fetal complications before initiating tocolytic Therapy (See Contraindications)
b. obtain NST
c. repeat U/S as needed to check fetal anatomy, size, amniotic fluid volume, and placentation; obtain transvaginal ultrasound for cervical length (see Step One)
d. monitor maternal status for infections, hypertensive disease, bleeding, etc.

Step Three

<u>If GA < 34 weeks</u>

-Initiate group B strep prophylaxis per GBS guideline
(see CDC 2010 Group B Streptococcal Disease: Perinatal Prevention)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm?CFID=9789024&CFTOKEN=269a59130de33407-032B3F82-C29E-D37D-63030BD510BC26C2&jsessionid=9a302f5118016b500ccf7355766d7a37573f (Accessed 4/22/16)

a. Tocolyze (regimens below)
b. Initiate neuroprotection (regimen below)
c. Administer corticosteroids

A single course of corticosteroids is recommended for pregnant women between 24 -34 wks and may be considered for pregnant women starting at 23 wks if they are at risk of delivering within 7 days.

betamethasone 12 mg IM x2 doses 24 hrs apart,
or
dexamethasone 6 mg IM x 4 doses 12 hours apart

'Rescue' steroids < 34kws and management of late preterm (34-37 wk) pregnancies (regimens below)

d. Liberally consult OB - GYN consultant re: management or transfer

Step Four

-Preterm labor education while hospitalized
-Outpatient management if medical adherence assured.
-Social Service, Mental Health, and Home Health Care consults may be appropriate.

Step Five

-If discharged, the patient should be seen in clinic on a weekly basis.
-Symptoms and adherence are re-assessed at each visit and cervical exam is considered at each encounter.
-Preterm labor recommendations are maintained until 34 weeks GA.

-Patients referred from outside an urban area remain in urban area until preterm labor is resolved. These patients should not transfer back to their Service Unit until their delivery could be safely managed by their local Level 1 Nursery, e. g., after 36 weeks. The patient should return to the Service Unit Hospital and not to their village. Notify referring provider prior to patients return to Service Unit.

A. Tocolysis

< 32 wks: Initiate tocolysis with non-steroidal anti-inflammatory

Indomethacin
There are RCTs and Cochrane reviews which support the use of Indomethacin

Indomethacin 50 mg po initially, followed by 25 mg po q4h for a maximum of 48 hours. Re-evaluate with an OB/GYN after a maximum of 400 mg total.

or

Ketorolac
There is less data to support the use of ketorolac, but it has been effective in our setting.

Administered ketorolac 30 mg loading dose followed by 30 mg every 6 hours for a maximum of 48 hours intravenously or intramuscularly

Contraindications — Maternal contraindications to cyclooxygenase inhibitors include platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma (in women with hypersensitivity to aspirin).

Ductal constriction appears to depend upon both gestational age and duration of exposure.

32-34 wks, if BP > 90/60

Nifedipine: An optimal nifedipine dosing regimen for treatment of preterm labor has not been defined.

A common approach is to administer an initial loading dose of 20 mg orally, followed by a second dose of 20 mg orally in 90 minutes. If contractions persist, 20 mg can be given orally every 6 hours for 48 hours, with a maximum dose of 180 mg/day.

The half-life of nifedipine is approximately two to three hours and the duration of action of a single orally administered dose is up to six hours. Plasma concentrations peak in 30 to 60 minutes. Nifedipine is almost completely metabolized in the liver and excreted by the kidney.

Contraindications — This agent has been associated with hypotension and headache. Calcium channel blockers are contraindicated in women with known hypersensitivity to the drug and should be used with caution in women with left ventricular dysfunction or congestive heart failure. The concomitant use of a calcium-channel blocker and

magnesium could theoretically act synergistically to suppress muscular contractility, which could result in respiratory paralysis, but despite extensive clinical use, this has rarely been encountered. Nifedipine may be used concomitantly with magnesium sulfate for neuroprotection (see below).

Triage therapy
Beta agonists
-For the management of acute preterm < 24 hours labor, terbutaline can also be administered subcutaneously by intermittent injection. The dose for intermittent injections is variable: 0.25 mg SQ and repeat q4h prn not to exceed 2 doses or until tocolysis is achieved. The drug should be withheld if the maternal heart rate is exceeds 120 beats/min.
Terbutaline is a good triage drug: if 1-2 doses over 4 hours abolish the contractions, it is unlikely that true preterm labor exists. A negative fFN and/or TVCL >2 cm should be able to confirm this impression.

-For anticipated > 24 hour therapy use other agents

Contraindications — Labor inhibition with a beta-adrenergic receptor agonist is relatively contraindicated among women with cardiac disease because of potent chronotropic effects. It can unmask undiagnosed CHD. Women with poorly controlled hyperthyroidism or diabetes mellitus should likewise not receive this class of labor inhibiting agents. Well-controlled diabetes mellitus is not a contraindication to beta-adrenergic receptor agonist therapy, as long as glucose and potassium concentrations are followed carefully and regulated. Beware of pulmonary edema.

Beta-adrenergic receptor agonists have important metabolic effects as well, including hypokalemia, hyperglycemia, and lipolysis. Glucose and potassium concentrations should be monitored during drug administration since hyperglycemia (140 to 200 mg/dL) and hypokalemia occur in 20 to 50 percent and 40 to 60 percent of patients, respectively.

CAUTION:
It is reasonable to consider beta-adrenergic agonists as agents for treatment of preterm labor. However, beta-adrenergic agents should not be the first choice in women with cardiac disease, diabetes mellitus, or hyperthyroidism.

By comparison, indomethacin should be avoided in the setting of maternal platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, or asthma (in women with hypersensitivity to aspirin). In these cases consider other agents.

B. Neuroprotection

See
1.) ANMC Magnesium Sulfate for Fetal Neuroprotection Guideline for complete details
2.) ACOG Patient Safety Checklist on Magnesium Sulfate, No. 7 (Appendix 1)

A. Indications

1. Women at 26*-32 weeks with preterm labor (defined as regular at least every 5 minutes uterine contractions accompanied by cervical change, and/or positive fetal fibronectin (fFN), and/or transvaginal ultrasound cervical length <1.5 cm) at or less than 32 weeks gestation, with either a singleton or twin pregnancy, who are expected to deliver within the next 24 hours.

2. Women with preterm premature rupture of membranes (PPROM) (documented by usual clinical criteria of pooling and ferning, and confirmed if necessary by oligohydramnios on ultrasound or a positive dye test), at or less than 32 weeks gestation, upon diagnosis and/ or in active labor.

B. Exclusions
1. Women with a short cervix on ultrasound not anticipated to deliver within 24 hrs.
2. Women with preterm contractions without cervical change, or women with a negative fFN.
3. Women who are being induced preterm for severe preeclampsia who would receive magnesium sulfate for a more prolonged period, and possibly at a different dose.
4. Women who have not delivered within 12 hours of admission for preterm labor or PPROM.
5. Women ≤ 25 weeks: only give 4 gm bolus and 1 gm per hour*

Magnesium sulfate is usually administered as a 6 g intravenous load over 20 minutes, followed by a continuous infusion of 2 g/hour x 12 hrs. This therapy can be repeated if recurrent PTL that may deliver within the next 24 hrs. This therapy is to increase neuroprotection for the fetus, not for tocolysis.

-Group B strep prophylaxis per GBS guideline
(see CDC 2010 Group B Streptococcal Disease: Perinatal Prevention)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm?CFID=9789024&CFTOKEN=269a59130de33407-032B3F82-C29E-D37D-63030BD510BC26C2&jsessionid=9a302f5118016b500ccf7355766d7a37573f (Accessed 4/22/16)

Contraindications — Magnesium sulfate is contraindicated in women with myasthenia gravis. . It also should not be used in women with known myocardial compromise or cardiac conduction defects because of its anti-inotropic effects.
Magnesium is eliminated by the kidneys, therefore women with impaired renal function may develop magnesium toxicity at the usual doses of administration. These women should receive the maintenance phase of treatment only if a patellar reflex is present (loss of reflexes being the first manifestation of symptomatic hypermagnesemia), respirations exceed 12 per minute, and the urine output exceeds 100 mL per four hours. Urine output and deep tendon reflexes should be closely monitored. Evaluation of serum magnesium concentration should be performed as needed.

Calcium gluconate (1 g intravenous slowly) may be administered to counteract magnesium toxicity.

'Rescue' Steroids < 34 wks
A single repeat course of antenatal corticosteroids should be considered in women whose prior course of corticosteroids was administered at 7 days previously and who remain at risk of preterm birth before 34 wks. However, regularly scheduled repeat courses or multiple courses (more than two) are not recommended.

Management of Late Preterm (> 34 wk < 37 wks)
1. In women with a singleton pregnancy between 34 weeks 0 days -36 weeks 6 days of gestation who are at high risk for PTB within the next 7 days (but before 37 weeks of gestation), we recommend treatment with betamethasone (two doses of 12 mg IM twenty four hours apart).

2. In women with preterm labor symptoms in the late preterm (LPT) period, please wait for evidence of preterm labor, such as a cervical dilatation of at least 3 cm or effacement of at least 75%, before treatment with betamethasone.

3. Late preterm antenatal corticosteroid administration should NOT be used in women diagnosed with chorioamnionitis.

4. Administration of late preterm antenatal corticosteroids should NOT be given if the pregnancy was already exposed to antenatal corticosteroids.

5. In women with LPT pregnancies receiving betamethasone, please avoid the use of tocolysis in an attempt to delay delivery to complete the steroid course since it is unclear if the benefits of betamethasone administration are outweighed by the risks of attempts to delay delivery.

6. In women with LPT pregnancies with a potential medical indication for delivery, betamethasone need not be given unless there is a definitive plan for LPT delivery.

7. These recommendation exclude patients with:
Pregestational diabetes, multifetal gestations, previous exposure to steroids during this pregnancy, or pregnancies with one major or two minor non-lethal fetal malformations. (see Appendix 2)

Summary of Recommendations

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

A single course of corticosteroids is recommended for pregnant women between 24 weeks of gestation and 34 weeks of gestation and may be considered for pregnant women starting at 23 wks if they are at risk of delivering within 7 days.

Accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation. Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in

accordance with one of the larger trials.

The evidence supports the use of first-line tocolytic treatment with beta-adrenergic agonist therapy, calcium channel blockers, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.

Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose.

Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with preterm labor and intact membranes.

The following recommendations and conclusions are based on limited and inconsistent scientific evidence (Level B):

A single course of repeat antenatal corticosteroids should be considered in women whose prior course of antenatal corticosteroids was administered at least 7 days previously and who remain at risk of preterm birth before 34 weeks of gestation.

Bed rest and hydration have not been shown to be effective for the prevention of preterm birth and should not be routinely recommended.

The positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms.

References:

- Management of preterm labor. Practice Bulletin No. 171. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;128:e155–64..

-Antenatal corticosteroid therapy for fetal maturation. Committee Opinion No. 677. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;128:e187–94.

-Use of prophylactic antibiotics in labor and delivery. Practice Bulletin No. 120. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:1472–83. (Reaffirmed 2016)

-Magnesium sulfate before anticipated preterm birth for neuroprotection. Committee Opinion No. 455. American College of Obstetricians and Gynecologists. Obstet Gynecol 2010;115:669–71. (Reaffirmed 2015)

-Prediction and prevention of preterm birth. Practice Bulletin No. 130. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:964–73. (Reaffirmed 2016)

-Patient Safety Checklist on Magnesium Sulfate Before Anticipated Preterm Birth for Neuroprotection, No. 7, American College of Obstetricians and Gynecologists August 2012

- Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD004352. DOI: 10.1002/14651858.CD004352.pub3.

- Flenady V, Wojcieszek AM, Papatsonis DNM, Stock OM, Murray L, Jardine LA, Carbonne B. Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD002255. DOI: 10.1002/14651858.CD002255.pub2.

-Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews Published Online: 8 OCT 2008, Assessed as up-to-date: 15 MAY 2006
Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub2.

-Schorr SJ, et al A comparative study of ketorolac (Toradol) and magnesium sulfate for arrest of preterm labor. South Med J. 1998 Nov;91(11):1028-32.

-ACOG Practice Advisory: Antenatal Corticosteroid Administration in the Late Preterm Period
http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Antenatal-Corticosteroid-Administration-in-the-Late-Preterm-Period (Accessed 4/22/16)

-SMFM Publications Committee. SMFM Statement: Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. Am J Obstet Gynecol 2016; DOI: 10.1016/j.ajog.2016.03.013.

-Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. NICHD Maternal-Fetal Medicine Units Network. N Engl J Med 2016; DOI: 10.1056/NEJMoa1516783.

Revised 10/30/16njm
9/26/16
4/22/16
10/6/15
8/14/13
5/2/13
2/7/11
3/2/02
10/26/98
7/31/97
10/11/95
10/1/94
1/15/88
6/1/80

Appendix 1

ACOG Patient Safety Checklist on Magnesium Sulfate, No. 7, August 2012

Use Rouse Regimen with exception ≤ 25 wks noted above

Appendix 2
(See Table 1 and Table 2)

Table 1: Major Fetal Anomalies / Congenital Malformations

(Need one major anomaly for exclusion)

Pulmonary
Congenital diaphragmatic hernia (CDH)
Congenital cystic adenomatoid malformation
Pleural effusions
Chylothorax
Bronchogenic cyst
Bronchpulmonary sequestration

Cardiac
Anomalous pulmonary venous return
Tricuspid atresia
Mitral atresia
Double right ventricle
Ebsteins's malformation
Pulmonary atresia
Hypoplastic left heart syndrome
Transposition of great vessels
Tetrology of fallot
Double outlet right ventricle
Aortic stenosis
Aortic coartation
Fetal arrhythmia (tachycardia, bradycardia, or supraventricular tachycardia)

Genito-urinary
Any genitor-urinary lesion accompanied by oligohydramnios at <24 wks
Bilateral renal agenesis
Cystic renal disease (polycystic or multicystic)
Obstructive uropathy
Horseshoe kidney
Megacystis microcolon
Cloacal abnormality

CNS
Anencephaly

Holoprosencephaly
Dandy-walker malformation or variant
Septo-optic dysplasia
Neural tube defect
Vein of Galen aneurysm

Skeletal
Acondrogenesis
Thanatophoric dysplasia
Osteogenesis imperfecta
Thoracic dysplasia
Hypophosphatemia
Short rib polydactyly
Any skeletal defect with suspected small thorax

Other
Any karyotype abnormality
Any suspected genetic syndrome
Cleft lip/palate
Micrognathia
Hydrops
Fetal anemia
Neck mass
Gastroschisis

Table 2: Minor Fetal Anomalies / Congenital Malformations

(Need two minor anomalies for exclusion)

Cardiac
ASD
VSD
Intracardiac echogenic focus

CNS
Choroid plexus cysts (unilateral or bilateral)
Mild ventriculomegaly (defined by a lateral ventricle measurement of <1.5cm)
Agenesis of the corpus callosum
Arachnoid cyst

Genito-urinary
Pyelectasis
Hydronephrosis
Unilateral renal agenesis (normal AFI)
Pelvic kidney
Hypospadias

Skeletal
Achondroplasia (with normal thoracic circumference)
Clubbed foot (unilateral or bilateral)

Other
Echogenic bowel (Cystic fibrosis negative)
Polydactyly