



## APEC Guidelines Preterm Labor

Prematurity is the leading cause of perinatal mortality in the US and is the major reason why we lag behind other developed nations in infant mortality rates. Approximately 70% of neonatal deaths, 36% of infant deaths, and 25-50% of cases of long-term neurologic impairment in children can be attributed to preterm birth. (ACOG, 2012a) The estimated cost of preterm births exceeds \$26.2 billion annually with an average cost of care for a preterm birth ten times greater than that of a full term birth, \$32,325 to \$3,325 respectively. (CDC, 2008) In 2010, preterm birth occurred in 12.0% of 4 million births in the US and 15.6% of 58,000 births in the state of Alabama. (Hamilton, 2011) While the preterm birth rate in Alabama has declined over the past 4 years (17.1% in 2006 to 15.6% in 2010), it has the second highest preterm birth rate in the nation. (Hamilton, 2011)

Preterm birth is defined as a birth between 20 0/7 and 36 6/7 weeks gestation. Risk factors for preterm birth include:

- Prior preterm birth
- African American race
- Age <17 or >35
- Low socioeconomic status
- Low pre-pregnancy weight (BMI < 18.6)
- Smoking, alcohol, or illicit drug use
- Multiple gestation
- Uterine anomaly

Approximately 50% of all preterm births are the result of preterm labor (PTL). (Berghella, 2010) PTL is defined as regular contractions ( $\geq 6/60$  min) with documented cervical change before the completion of 37 weeks gestation. The pathophysiological triggers for PTL are largely unknown but may include decidual hemorrhage (abruption), mechanical factors (uterine over distention or cervical incompetence), hormonal changes (perhaps mediated by fetal or maternal stress) and inflammation/infection. A number of signs and symptoms have been suggested as predictors of preterm birth:

- Frequent uterine contraction ( $\geq 6$  in 60 min)
- Pelvic pressure
- Increased vaginal discharge
- Diarrhea
- Backache
- Cramping

Neither fetal fibronectin screening nor bacterial vaginosis testing have been shown to be useful screening tests for use in asymptomatic women at risk for preterm birth. Similarly, home uterine activity monitoring has not been found to be a beneficial or cost-effective test for evaluating women, either symptomatic or asymptomatic, at risk for preterm labor. These tests are not recommended as screening strategies for asymptomatic, at risk women. (ACOG, 2012a)

Fetal fibronectin assessment in women who present with symptoms of preterm labor may be useful in identifying women at highest risk for preterm delivery. Although the positive predictive value of fetal

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fibronectin for preterm delivery is overall low, the negative predictive value for delivery in the next 7-14 days is in excess of 95%. Therefore, women who present with symptoms of preterm labor but have cervical dilation <3 and a negative fetal fibronectin result are unlikely to deliver in the next 7-14 days and would likely not benefit from tocolysis and corticosteroid administration. (Goldenberg et al., 1997) Although several studies have failed to show a difference in effectiveness between fetal fibronectin testing and provider decision making with regard to admission in academic medical centers, the cost-effectiveness and utility may be more favorable in other practice settings. (Peaceman et al., 1997)

### **Treatment of Women at risk for Preterm Birth**

It is difficult to identify women who will ultimately deliver preterm since 30% of preterm labor spontaneously resolves and 50% of women hospitalized for preterm labor deliver at term. (ACOG, 2012a) Appropriate and prompt treatment of women who present in preterm labor is critical because it represents an opportunity to provide interventions aimed at improving maternal and fetal outcomes. These interventions include:

- Maternal tocolytic therapy
- Antenatal corticosteroids (ANCS)
- GBS prophylaxis
- Magnesium sulfate for fetal neuroprotection in pregnancies < 32 weeks gestation
- Transport to a facility with the appropriate level of neonatal care

### **Tocolysis**

In women at risk for preterm delivery, tocolysis should be initiated with the goal of preventing imminent preterm birth to allow time for corticosteroid treatment, transport of mother and fetus to a center with the appropriate level of care, antibiotic prophylaxis for GBS, and magnesium sulfate administration for fetal neuroprotection. Suggested tocolytic agents are listed in Appendix A. Evidence is lacking on beneficial effect of tocolytics beyond the time for corticosteroid administration and there are no convincing data demonstrating greater efficacy of one agent over another.

In 2011, the US FDA issued a warning regarding the use of terbutaline to treat PTL because of maternal side effects (FDA, 2011); thus terbutaline should not be used as a tocolytic agent other than as acute therapy for preterm contractions without labor (e.g. 1-2 subcutaneous doses for preterm contractions). (ACOG, 2012a)

There is no evidence to support routine use of maintenance oral tocolytic treatment following an episode of preterm labor arrested by acute tocolysis. Moreover, infusion pumps with terbutaline have not been shown to prolong gestation and should not be utilized in light of the recent FDA warnings.

### **Antenatal Corticosteroids**

The most beneficial intervention for improvement of neonatal outcomes among patients who give birth preterm is the administration of antenatal corticosteroids (ANCS). (ACOG, 2012a, 2012b) ANCS

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have been found to reduce the risk of neonatal death, intraventricular hemorrhage, and respiratory distress syndrome in the preterm neonate. A single course is recommended for women at risk for preterm birth that is between 24 and 34 weeks gestation. (ACOG, 2012a) Betamethasone and dexamethasone are the most widely studied and preferred ANCS; either is acceptable treatment. Data on treatment of women with intact membranes support the use of ANCS up to 34 weeks. However, in the subset of women with PROM at 32-33 weeks, the benefit is less clear. Based on this, the NIH Consensus conference felt there was insufficient evidence to recommend routine corticosteroid administration to women with PROM at 32-33 weeks. Given the potential benefit and minimal risk in the absence of a contraindication, justification can be made for a uniform upper GA threshold of 34 weeks regardless of membrane status for corticosteroid administration which would be easier to implement and ensure that all patients who could benefit are receiving treatment. Given the increasing survival of 23-24 week infants, many neonatologists advocate extending the window for corticosteroid administration to 23 weeks. (Carlo et al., 2011) In the absence of maternal contraindications, this should be considered.

### Antenatal Corticosteroid Regimens

ANCS Drug	Dosage
Betamethasone	Two 12mg IM injections 24 hours apart
Dexamethasone	Four 6 mg IM injections 12 hours apart

Although the greatest benefit appears to be between 48 hours and 7 days after treatment, ANCS treatment for less than 24 hours has been associated with reductions in neonatal morbidity and mortality. A first dose of ANCS should be administered even if the ability to give the second dose is unlikely based on the clinic scenario. (ACOG, 2012a)

A second course of ANCS should be considered in women whose prior course of ANCS was administered at least 7 days previously and who remain at risk for PTB before 34 weeks GA. (ACOG, 2012a) Multiple repeat courses are associated with reductions in birthweight and head circumference without an improvement in neonatal outcomes.

### Group B Streptococcal Treatment

If the patient has a positive antepartum GBS culture, she should receive appropriate antibiotic prophylaxis for GBS intrapartum. If the results are unavailable, the patient should receive intrapartum prophylaxis as per CDC recommendations. See the GBS guideline for further details.

### Magnesium Sulfate for Cerebral Palsy protection

Magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks GA. (ACOG, 2012a; Crowther, Hiller, & Doyle, 2002; Rouse et al., 2008) See MgSO<sub>4</sub> APEC guideline # 11.

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### Transport to tertiary facility

In order to maximize perinatal outcomes, delivery of preterm infants should occur at facilities capable of providing the appropriate level of neonatal resuscitative and supportive care commensurate with the gestational age. The American Academy of Pediatrics has recently redefined levels of neonatal care providing recommendations to ensure each newborn infant is delivered and cared for in a facility most appropriate for his or her needs, see Table 1: Levels of Neonatal Care. (Pediatrics, 2012) The importance of place of delivery is underscored by the improved survival of these neonates when delivered at tertiary care centers. (Cunningham et al., 2010)

**Table 1: Levels of Neonatal Care**

Level of Care	Capabilities	Health Care Provider Types
<b>Level I Well newborn nursery</b>	<ul style="list-style-type: none"> <li>Provide neonatal resuscitation at every delivery</li> <li>Evaluate and provide postnatal care to stable term newborn infants</li> <li>Stabilize and provide care for infants born 35-37 weeks GA who remain physiologically stable</li> <li>Stabilize newborn infants who are ill and those born at &lt; 35 wks gestation until transfer to a higher level of care</li> </ul>	<ul style="list-style-type: none"> <li>Pediatricians, family physicians, nurse practitioners, and other advanced practice registered nurses</li> </ul>
<b>Level II Special care nursery</b>	Level I capabilities plus: <ul style="list-style-type: none"> <li>Provide care for infants born <math>\geq 32</math> wks GA and weighing <math>\geq 1500</math> g who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis</li> <li>Provide care for infants convalescing after intensive care</li> <li>Provide mechanical ventilation for brief duration (&lt;24 h) or continuous positive airway pressure or both</li> <li>Stabilize infants born before 32 wk gestation and weighing &lt; 1500 g until transfer to a neonatal intensive care facility</li> </ul>	<ul style="list-style-type: none"> <li>Level I health care providers plus: Pediatric hospitalists, neonatologists, and neonatal nurse practitioners</li> </ul>
<b>Level III NICU</b>	Level II capabilities plus: <ul style="list-style-type: none"> <li>Provide sustained life support</li> <li>Provide comprehensive care for infants born &lt; 32 wks GA and weighing &lt; 1500 g and born at all GA and birth weights with critical illness</li> <li>Provide prompt and readily available access to a full range of pediatric medical subspecialists, and pediatric ophthalmologists</li> <li>Provide a full range of respiratory support that may include conventional and/or high-frequency ventilation and inhaled nitric oxide</li> <li>Perform advanced imaging, with interpretation on an urgent basis, including computed tomography, MRI, and echocardiography</li> </ul>	<ul style="list-style-type: none"> <li>Level II health care providers plus: Pediatric medical subspecialists, pediatric anesthesiologists, pediatric surgeons, and pediatric ophthalmologists</li> </ul>
<b>Level IV Regional NICU</b>	Level III capabilities plus: <ul style="list-style-type: none"> <li>Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions</li> <li>Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site</li> <li>Facilitate transport and provide outreach education</li> </ul>	<ul style="list-style-type: none"> <li>Level III health care providers plus: Pediatric surgical subspecialists</li> </ul>

(Pediatrics, 2012)

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### OB Management

After assessment of the patient's symptoms, history and physical exam, determine whether the patient has preterm contractions, preterm labor, premature rupture of membranes, or other diagnosis.

Preterm labor diagnosis is often difficult but generally requires:

- $\geq 6$  contractions per hour with documented cervical change
- OR**
- Cervical dilatation  $\geq 2$  cm and 75% effaced with a history of contractions

Gestational Age	Management
<b>Late Preterm (34 - 36 weeks)</b>	<ul style="list-style-type: none"> <li>• GBS prophylaxis as indicated based on culture or CDC risk stratification if culture data unavailable</li> <li>• Delivery at appropriate level facility</li> </ul>
<b>Preterm (32 - 33 weeks)</b>	<ul style="list-style-type: none"> <li>• Initiate tocolysis</li> <li>• Antenatal corticosteroids if not previously administered</li> <li>• Consider repeat ANCS in women whose prior course was administered at least 7 days previously and who remain at risk for PTB before 34 weeks</li> <li>• GBS prophylaxis as indicated based on culture or CDC risk stratification if culture data unavailable</li> <li>• Delivery at Level III or higher facility</li> </ul>
<b>Preterm (23 - 31 weeks)</b>	<ul style="list-style-type: none"> <li>• Initiate tocolysis</li> <li>• Antenatal corticosteroids if not previously administered</li> <li>• Consider repeat ANCS in women whose prior course was administered at least 7 days previously and who remain at risk for PTB before 34 weeks</li> <li>• GBS prophylaxis as indicated based on culture or CDC risk stratification if culture data unavailable</li> <li>• Delivery at Level III or higher facility</li> <li>• Magnesium sulfate infusion for neuroprotection</li> </ul>
<b>Less than 23 weeks</b>	<ul style="list-style-type: none"> <li>• Patient counseling and consultation with maternal fetal medicine specialist</li> </ul>

### Quality Indicators/Benchmarks

- Delivery at appropriate level facility
- Antenatal corticosteroid administration < 34 weeks GA
- GBS prophylaxis

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### Appendix A

Tocolytic Agent	Dosage	Contraindications	Maternal AEs	Fetal/Neonatal AEs
<b>Beta-adrenergic receptor agonists</b>  <b>Terbutaline</b>	Terbutaline: 0.25 mg subcutaneously not more frequently than every 20 min (hold for pulse >120/min) and limited to a maximum of 2 doses for preterm contractions	Tachycardia-sensitive maternal cardiac disease and poorly controlled diabetes mellitus	Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia	Fetal tachycardia
<b>Magnesium Sulfate</b>	4-6 gram bolus for 20 min then 2-3 grams/hr	Myasthenia gravis; avoid prolonged concomitant use with calcium channel blockers	Flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema, cardiac arrest	Lethargy, hypotonia, respiratory depression, bone demineralization with prolonged use
<b>Calcium channel blockers</b>	30 mg loading dose, then 10-20 mg every 4-6 hrs for 24-48 hrs	Cardiac disease, use caution with renal disease, hypotension (<90/50), avoid prolonged concomitant use with MgSO <sub>4</sub>	Dizziness, flushing, hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with MgSO <sub>4</sub> ; and elevation of hepatic transaminases	No known AEs
<b>Nonsteroidal anti-inflammatory drugs</b> <b>Indomethacin</b>	Indomethacin: loading dose 50 mg rectally or 50-100 mg orally, then 25-50 mg orally every 6 hr x 48 hr	Platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma (in women with hypersensitivity to aspirin)	Nausea, heartburn	In utero constriction of ductus arteriosus, oligohydramnios, and NEC in preterm newborns. The risk of premature closure of the ductus arteriosus increases with advancing GA, therefore its use should be limited to < 32 wk.

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#### References

- ACOG. (2012a). Management of Preterm Labor Practice Bulletin 127. [Practice Bulletin No. 127]. *The American College of Obstetricians and Gynecologists*.
- ACOG. (2012b). Prediction and Prevention of Preterm Birth Practice Bulletin 130. [Practice Bulletin]. *The American College of Obstetrics and Gynecologists*.
- Berghella, V. (2010). Preterm Labor. In J. T. Queenan, J. C. Hobbins & C. Y. Spong (Eds.), *Protocols for High-Risk Pregnancies* (5th ed.). West Sussex, UK: Wiley-Blackwell.
- Carlo, W. A., McDonald, S. A., Fanaroff, A. A., Vohr, B. R., Stoll, B. J., Ehrenkranz, R. A., . . . Human Development Neonatal Research, N. (2011). Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. [Research Support, N.I.H., Extramural]. *JAMA*, *306*(21), 2348-2358. doi: 10.1001/jama.2011.1752
- CDC. (2008). *Final Natality Data*. Hyattsville, MD.
- Crowther, C. A., Hiller, J. E., & Doyle, L. W. (2002). Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*(4), CD001060. doi: 10.1002/14651858.CD001060
- Cunningham, F. G., Leveno, K. J., Bloom, S. L., Hauth, J. C., Rouse, D. J., & Spong, C. Y. (2010). *Williams Obstetrics* (23rd ed.). New York, USA: McGraw-Hill.
- FDA. (2011). *FDA drug safety communication: new drug warnings against use of terbutaline to treat preterm labor*. Silver Springs, MD: FDA Retrieved from <http://www.fda.gov/Drugs/DrugSafety/ucm243539.htm> October 19, 2012.
- Goldenberg, R. L., Mercer, B. M., Iams, J. D., Moawad, A. H., Meis, P. J., Das, A., . . . Bottoms, S. F. (1997). The preterm prediction study: patterns of cervicovaginal fetal fibronectin as predictors of spontaneous preterm delivery. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol*, *177*(1), 8-12.
- Hamilton, B. E., Martin, J.A., Ventura, M.A. (2011). Births: Preliminary Data for 2010. *DHHS CDC National Center for Health Statistics*, *60*(2).
- Peaceman, A. M., Andrews, W. W., Thorp, J., Cliver, S., Lukes, A., Iams, J., . . . Pietrantonio, M. (1997). Fetal fibronectin as a predictor of preterm birth in patients with symptoms: A multicenter trial. *American Journal of Obstetrics and Gynecology*, *177*, 13-18.
- Pediatrics, A. A. o. (2012). Levels of Neonatal Care. [Policy Statement]. *Pediatrics*, *130*, 587-597.
- Rouse, D. J., Hirtz, D. G., Thom, E., Varner, M. W., Spong, C. Y., Mercer, B. M., . . . Eunice Kennedy Shriver, N. M.-F. M. U. N. (2008). A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med*, *359*(9), 895-905. doi: 10.1056/NEJMoa0801187