



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, 2016) 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 2015, preterm birth occurred in 9.6% of approximately 4 million births in the US and 11.7% of 59,632 births in the state of Alabama. (Hamilton, Martin, & Osterman, 2016) The preterm birth rate in Alabama has increased slightly over the past year (11.66 % in 2014 to 11.73% in 2015) and Alabama has the third highest preterm birth rate in the nation. (Hamilton et al., 2016)

Preterm birth is defined as a birth between 20 0/7 and 36 6/7 weeks gestation based on the obstetric estimate. 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 (≥ 6 in 60 min)
- Pelvic pressure
- Increased vaginal discharge
- Diarrhea
- Backache
- Cramping

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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, 2016)

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 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, 2016) Appropriate and prompt treatment of women who present in preterm labor is critical because it represents an opportunity to provide interventions aimed at improving perinatal 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

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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 an intermittent acute therapy for preterm contractions without labor (e.g. 1-2 subcutaneous doses for preterm contractions) or in the setting of uterine tachysystole. (ACOG, 2016)

There is no evidence to support routine use of maintenance oral tocolytic treatment following an episode of preterm labor arrested by acute tocolysis nor as prophylaxis in a woman with a history of preterm birth. 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, 2012, 2016) ANCS have been found to reduce the risk of neonatal death, intraventricular hemorrhage, and respiratory distress syndrome in the preterm neonate. ACOG Practice Bulletin # 159 states “A single course of ANCS is recommended for women at risk for preterm birth that is between 24 and 34 weeks gestation, and may be considered for pregnant women starting at 23 weeks gestation, who are at risk of preterm delivery within 7 days.” (ACOG, 2016) Betamethasone and dexamethasone are the most widely studied and preferred ANCS; either is acceptable treatment.

Antenatal Corticosteroid Regimen

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, 2016) In patients with progressive labor, who have received their first but not second dose of ANCS, there is no proven utility to accelerating the timeline for giving the second dose, i.e. there is no proven benefit to giving the second dose at 12 instead of 24 hours.

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A single repeat course of ANCS should be considered in women whose prior course of ANCS was administered at least 14 days previously and who remain at high risk for PTB before 34 weeks GA. (ACOG, 2016) Multiple repeat courses are not recommended since they are associated with reductions in birthweight and head circumference without an improvement in neonatal outcomes.

ANCS in Patients at Risk for Late Preterm Delivery

The 2016 NICHD Maternal Fetal Medicine Units Network “Antenatal betamethasone for women at risk for late preterm delivery” publication demonstrated significant benefit for neonates at risk of being born in the late preterm period (34 0/7 weeks to 36 6/7 weeks of gestation). (Gyamfi-Bannerman et al., 2016) Study outcomes show a lower incidence of respiratory support in the first 72 hours of life and fewer severe respiratory complications in the betamethasone group. **APEC recommends one course of betamethasone at 34 0/7 to 36 5/7 weeks (if not previously administered) for patients who have a high probability of delivery occurring in the late preterm period.** This is defined as one of the following:

- Preterm labor with cervical dilation > 2 cm.
- Spontaneous rupture of membranes.
- Hypertensive disease of pregnancy with high likelihood of delivery occurring \leq 36 6/7 weeks.
- Other individualized situations with a high probability of delivery \leq 36 6/7 weeks (examples: prior myomectomy or classical incision, intrauterine growth restriction, oligohydramnios, placenta previa or accreta, or nonreassuring fetal testing not requiring immediate delivery).

See the APEC Antenatal Corticosteroids in Women at risk for Late Preterm Birth guideline for additional details.

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 APEC GBS guideline for additional 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, 2016; Crowther, Hiller, & Doyle,

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2002; Rouse et al., 2008) See the APEC Magnesium Sulfate for Fetal Neuroprotection guideline for additional details.

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)

March of Dimes

The March of Dimes published a Preterm Labor Assessment Toolkit, it can be accessed here <http://www.marchofdimes.org/>

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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:

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

Gestational Age	Management
Late Preterm (34 - 36 weeks)	<ul style="list-style-type: none"> • Antenatal corticosteroids if not previously administered. • GBS prophylaxis as indicated based on culture or CDC risk stratification if culture data unavailable. • Delivery at appropriate level facility.
Preterm (32 - 33 weeks)	<ul style="list-style-type: none"> • Initiate tocolysis. • Antenatal corticosteroids if not previously administered. • Consider repeat ANCS in women whose prior course was administered at least 14 days previously and who remain at risk for PTB before 34 weeks. • GBS prophylaxis as indicated based on culture or CDC risk stratification if culture data unavailable. • Delivery at Level III or higher facility.
Preterm (23 - 31 weeks)	<ul style="list-style-type: none"> • Initiate tocolysis. • Antenatal corticosteroids if not previously administered. • Consider repeat ANCS in women whose prior course was administered at least 14 days previously and who remain at risk for PTB before 34 weeks. • GBS prophylaxis as indicated based on culture or CDC risk stratification if culture data unavailable. • Delivery at Level III or higher facility. • Magnesium sulfate infusion for fetal neuroprotection.
Less than 23 weeks	<ul style="list-style-type: none"> • Patient counseling and consultation with maternal fetal medicine specialist.

Quality Indicators/Benchmarks

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

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Table 1: Levels of Neonatal Care

Level of Care	Capabilities	Health Care Provider Types
Level I Well newborn nursery	<ul style="list-style-type: none"> • Provide neonatal resuscitation at every delivery • Evaluate and provide postnatal care to stable term newborn infants • Stabilize and provide care for infants born 35-37 weeks GA who remain physiologically stable • Stabilize newborn infants who are ill and those born at < 35 wks gestation until transfer to a higher level of care 	<ul style="list-style-type: none"> • Pediatricians, family physicians, nurse practitioners, and other advanced practice registered nurses
Level II Special care nursery	<p>Level I capabilities plus:</p> <ul style="list-style-type: none"> • Provide care for infants born \geq 32 wks GA and weighing \geq 1500 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 • Provide care for infants convalescing after intensive care • Provide mechanical ventilation for brief duration (<24 h) or continuous positive airway pressure or both • Stabilize infants born before 32 wk gestation and weighing < 1500 g until transfer to a neonatal intensive care facility 	<ul style="list-style-type: none"> • Level I health care providers plus: Pediatric hospitalists, neonatologists, and neonatal nurse practitioners
Level III NICU	<p>Level II capabilities plus:</p> <ul style="list-style-type: none"> • Provide sustained life support • Provide comprehensive care for infants born < 32 wks GA and weighing < 1500 g and born at all GA and birth weights with critical illness • Provide prompt and readily available access to a full range of pediatric medical subspecialists, and pediatric ophthalmologists • Provide a full range of respiratory support that may include conventional and/or high-frequency ventilation and inhaled nitric oxide • Perform advanced imaging, with interpretation on an urgent basis, including computed tomography, MRI, and echocardiography 	<ul style="list-style-type: none"> • Level II health care providers plus: Pediatric medical subspecialists, pediatric anesthesiologists, pediatric surgeons, and pediatric ophthalmologists
Level IV Regional NICU	<p>Level III capabilities plus:</p> <ul style="list-style-type: none"> • Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions • Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site • Facilitate transport and provide outreach education 	<ul style="list-style-type: none"> • Level III health care providers plus: Pediatric surgical subspecialists

(Pediatrics, 2012)

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Appendix A

Tocolytic Agent	Dosage	Contraindications	Maternal AEs	Fetal/Neonatal AEs
Beta-adrenergic receptor agonists Terbutaline	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, hyperglycemia	Fetal tachycardia
Magnesium Sulfate	4-6 gram bolus over 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
Calcium channel blockers	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 MgSO4	Dizziness, flushing, hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with MgSO4; elevation of hepatic transaminases	No known AEs
Nonsteroidal anti-inflammatory drugs Indomethacin	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. The risk of oligohydramnios increases with duration of use therefore, RX should be limited to 48-72 hours.

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