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How to manage emergencies associated with tocolysis for preterm labor

Although short-term tocolysis usually is safe, certain agents and scenarios may increase the risk of harm. Here, four cases involving serious complications.

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CASE 1 Preterm labor with cervical changes

Ms. M, a 42-year-old woman pregnant with her second child, begins having contractions at 30 weeks' gestation. Examination reveals that her cervix is dilated 2 cm and effaced 50%. She is given subcutaneous terbutaline to suppress her contractions. Thirty minutes later, she complains of shortness of breath and chest pain. An electrocardiogram reveals depression of the ST segment, and a chest radiograph shows mild pulmonary edema.

How should her symptoms be managed?

Preterm labor precedes delivery in about 50% of preterm births. Approximately 33% of women who have preterm labor will experience spontaneous resolution, and more than 50% of women who have preterm labor will deliver at term. Although the use of tocolytic therapy has proved to be effective at temporarily suppressing uterine activity, it has not been shown to delay delivery for more than a few hours or days.[1]

The American College of Obstetricians and Gynecologists (ACOG) recommends the use of tocolytics only when a delay in labor for approximately 48 hours would improve outcome. Therefore, tocolytic therapy should be reserved for the following circumstances:

- to stop the progress of labor long enough to administer antenatal corticosteroid therapy
- to prolong pregnancy when there is an underlying self-limiting condition that can cause labor, such as pyelonephritis
- to provide time for safe transport to a facility with a higher level of neonatal care.[2]

Tocolytics are generally not indicated before the fetus is viable, although we lack data from randomized, controlled trials to support a specific recommendation. The approach is clearer when the fetus is near the upper limits of viability. Most studies suggest that 34 weeks' gestation is the threshold at which the perinatal morbidity and mortality associated with delivery are too low to justify the cost and potential complications of tocolysis.[3]

Women who experience preterm labor without cervical changes generally should not be treated with tocolytics.[2] Contraindications to tocolytic therapy include:

- lethal fetal anomaly
- nonreassuring fetal status
- maternal disease

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ILLUSTRATION: SHARON AND JOEL HARRIS FOR OBG MANAGEMENT

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- maternal hemorrhage with hemodynamic instability.

Beta-adrenergic agonists carry many risks

These agents have been studied in several randomized, controlled trials. Although ritodrine was approved as tocolytic therapy by the US Food and Drug Administration (FDA), it has since been removed from the US market. Terbutaline is still available but lacks FDA approval as a tocolytic.

Maternal side effects associated with beta-adrenergic agonists are thought to arise from stimulation of the beta-1 and beta-2 adrenergic receptors. Stimulation of the former increases maternal heart rate and stroke volume, whereas stimulation of the beta-2 adrenergic receptors causes the relaxation of smooth muscle, including the muscles of the myometrium, blood vessels, and bronchial tree. The resulting symptoms may include maternal tachycardia, cardiac arrhythmias, palpitations, and metabolic aberrations (including hyperglycemia, hypokalemia, and hypotension). Common symptoms associated with the administration of a beta-adrenergic agonist include tremor, shortness of breath, and chest discomfort.[4] Although pulmonary edema and myocardial ischemia are uncommon, they can occur even when there is no history of underlying maternal disease.

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Common maternal symptoms associated with administration of a beta-adrenergic agonist include tremor, shortness of breath, and chest discomfort

Terbutaline has been linked to maternal deaths

Sixteen maternal deaths were reported following initial marketing of terbutaline in 1976 until 2009. Three of the 16 cases involved outpatient use of terbutaline administered by a subcutaneous pump, and nine cases involved use of oral terbutaline alone or in addition to subcutaneous or IV terbutaline. In addition, 12 cases of serious maternal cardiovascular events were reported in association with terbutaline. These events included cardiac arrhythmias, myocardial infarction, pulmonary edema, hypertension, and tachycardia.

Because of these events, **the FDA issued a black box warning for terbutaline that prohibits its use in the treatment of preterm labor for longer than 48 to 72 hours in the inpatient or outpatient setting because of the potential for serious maternal heart problems and death.[5] Oral terbutaline should be avoided entirely in the prevention and treatment of preterm labor. However, the use of terbutaline for the management of acute tachysystole with an abnormal fetal heart-rate (FHR) pattern remains a reasonable course of treatment.[6]**

Fetal tachycardia is the most common side effect of beta-adrenergic receptor agonists. For this reason, use of these drugs is not recommended when changes in FHR may be the first sign of fetal compromise, such as in patients with hemorrhage or infection. Neonatal hypoglycemia may also occur if maternal hyperglycemia is not controlled.[7]

CASE 1 Resolved

Terbutaline is discontinued, and the patient's pulmonary edema is treated with a single dose of furosemide. Electrolyte abnormalities resolve with discontinuation of medication. The patient stabilizes. Once her cardiorespiratory status improves, her contractions lessen and the cervix remains unchanged. She requires no further tocolysis and is discharged home. She presents again at 38 weeks in spontaneous labor.

CASE 2 Preterm labor treated with indomethacin

Ms. J, age 23, is 26 weeks' pregnant with her first child. When she experienced preterm labor at 24.5 weeks' gestation, she was given indomethacin. Now, ultrasonographic imaging reveals decreased amniotic fluid volume.

How should she be managed?

Indomethacin is a cyclooxygenase (COX) inhibitor. These drugs reduce prostaglandin production through the general inhibition of cyclooxygenase or by a specific receptor.[8] Indomethacin is the most commonly used tocolytic in this class. It is a nonspecific COX inhibitor, as opposed to a COX-2 inhibitor.

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The latter has been associated with serious adverse outcomes in the nonobstetric population. COX-2 inhibitors now carry a black box warning or are no longer available.

Maternal contraindications for COX inhibitors include asthma, bleeding disorders, and significant renal dysfunction.

Although maternal side effects with COX inhibitors are usually mild, fetal side effects may be serious enough to cause perinatal morbidity or death.[9]

How indomethacin can lead to oligohydramnios

Maternal administration of indomethacin or ibuprofen can reduce fetal urine output and decrease the volume of amniotic fluid. In most cases, oligohydramnios occurs when indomethacin or ibuprofen has been given for more than 72 hours. For this reason, long-term use of a COX inhibitor should be accompanied by frequent monitoring of amniotic fluid volume by ultrasonography.

The most serious fetal complication associated with prolonged indomethacin administration (longer than 72 hours) is premature constriction of the ductus arteriosus. Ductal constriction appears to be contingent on gestational age. It has been described as early as 24 weeks' gestation but is most common after 31 or 32 weeks. Therefore, indomethacin is not recommended for use after 32 weeks' gestation.[10]

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Concomitant use of a calcium-channel blocker and magnesium sulfate can sometimes lead to neuromuscular blockade and significant respiratory depression

CASE 2 Resolved

The indomethacin is discontinued as soon as the decreased amniotic fluid is noted. The fluid volume returns to normal over the next 3 to 5 days. Because of the early gestational age, nifedipine is given to suppress contractions, and the patient has no further complications.

CASE 3 Preterm labor and magnesium intoxication

Ms. K experiences contractions and rapid cervical change at 32 weeks' gestation. She is given magnesium for the preterm labor and fetal neuroprophylaxis, with nifedipine, a calcium-channel blocker, added as second-line tocolysis. Approximately 8 hours later, she reports difficulty breathing and moving.

How should her obstetrician proceed?

Calcium-channel blockers such as nifedipine are used for acute and maintenance tocolysis. This class of drugs is often selected for its relative ease of use and safety, as it has few maternal and fetal side effects. However, concomitant use of a calcium-channel blocker and magnesium sulfate can sometimes lead to neuromuscular blockade and significant respiratory depression, even necessitating mechanical ventilation.[9] Treatment of these effects includes IV administration of 10% calcium gluconate (5–10 mEq), which usually reverses respiratory depression and heart block caused by magnesium intoxication. In extreme cases, peritoneal dialysis or hemodialysis may be required.

CASE 3 Resolved

The patient is given 10% calcium gluconate in the dosage described above, and she stabilizes. However, her contractions continue and she delivers at 32 weeks' gestation. The infant does well in the NICU.

CASE 4 Preterm labor in a woman with kidney dysfunction

Ms. F, age 40, presents at 30 weeks' gestation with regular contractions and cervical dilation of more than 3 cm. She also reports a history of kidney disease.

What steps are recommended prior to the initiation of magnesium therapy?

Magnesium sulfate has been used for more than 40 years to treat preterm labor and is still considered a first-line therapy in many centers. Although maternal side effects usually are mild, an adverse event may occur if the patient is not monitored carefully. An absence of deep-tendon reflexes should alert the clinician that magnesium levels need to be measured. Reflexes usually are lost at a serum level of 10 mEq/L or higher. When the magnesium level exceeds 13 mEq/L, cardiac

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arrest is a risk. IV calcium should be administered immediately in such patients.

Magnesium should be used with caution in patients with myocardial compromise. Because magnesium is eliminated by the kidneys, women with impaired renal function may experience magnesium toxicity at normal doses. If a patient has a creatinine level above 1 mg/dL, consider alternative treatment for her preterm labor. If magnesium is given, the normal loading dose (4–6 g) is appropriate, but the maintenance dose should be reduced.[11]

Fetal effects of magnesium sulfate

Recent studies indicate that predelivery magnesium may offer fetal neuroprotection. The minimum duration of administration for such neuroprotection is unknown but is less than 24 hours.[8]

Although magnesium can alter FHR patterns slightly, these changes are not clinically significant. Magnesium can also cause mild neonatal suppression at the time of delivery, but its effects quickly resolve with appropriate neonatal resuscitation. Long-term (>5 days) therapy is not recommended.

In May 2013, the FDA issued a warning about the risk of neonatal complications with long-term maternal magnesium administration. These complications include osteopenia, low calcium, and bone fracture. The pregnancy category for magnesium sulfate will be changed from "A" to "D" because of these teratogenic effects.[12]

CASE 4 Resolved

Because magnesium is mainly cleared by renal excretion, the clinician administers the medication with caution in this patient with reduced renal function. The clinician administers the same 4- to 6-g bolus that would be given a patient with normal kidney function, but the maintenance dose is reduced to 1 g. Magnesium levels are obtained every 12 hours or when clinically indicated.

Bottom line: Be ready to act

The short-term use of tocolytic therapy usually is not associated with maternal or fetal complications. After initial administration, maintenance tocolytic therapy probably does not prolong gestation.

Given the potential for harm without additional fetal benefit associated with extended therapy, I recommend that clinicians follow current clinical guidelines from ACOG for use of tocolytic agents. In the process, be vigilant for complications and be ready to act appropriately. Keep maternal and fetal conditions in mind when selecting a tocolytic agent.

FAST TRACK

Predelivery magnesium may offer fetal neuroprotection, but long-term administration is associated with fetal complications

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