Inhibition of acute preterm labor

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INTRODUCTION

Preterm labor leading to preterm birth is a significant cause of morbidity and mortality in infants. Tocolysis may enable pregnancy prolongation, at least over the short term, and thus provide time for further in utero maturation and interventions that may improve infant outcome.

This topic will discuss the use of tocolytic drugs for inhibition of acute preterm labor. Other issues related to preterm labor, including pathogenesis, risk factors, clinical manifestations and diagnosis, diagnostic evaluation, prevention, and neonatal outcome, are reviewed separately.

- (See "Preterm birth: Risk factors, interventions for risk reduction, and maternal prognosis".)
- (See "Preterm labor: Clinical findings, diagnostic evaluation, and initial treatment".)

EFFICACY

Administration of tocolytic drugs can reduce the strength and frequency of uterine contractions. In women with acute preterm labor, a 2009 meta-analysis of randomized trials found that these drugs were more effective than placebo/control for delaying delivery for 48 hours (75 to 93 percent versus 53 percent for placebo/control) and for seven days (61 to 78 percent versus 39 percent for placebo/control), but not for delaying delivery to 37 weeks [1].

Notably in this meta-analysis [1] and others [2], a substantial proportion of women diagnosed with preterm labor (approximately 50 percent) and not treated with tocolytics did not go on to deliver in the short term or even preterm. Furthermore, women treated with tocolytics did not achieve statistically significant reductions in important newborn clinical outcomes, such as respiratory distress and survival [1].

TREATMENT GOALS

Given the limited ability of tocolytic therapy to delay delivery for a prolonged period of time, the major goals of treatment of acute preterm labor are to [3]:

- Delay delivery by at least 48 hours (when safe to do so) so that antenatal corticosteroids (primary or rescue) administered to the mother have time to achieve their maximum fetal/neonatal effects. Predelivery administration of betamethasone reduces the risk of neonatal death, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis in preterm neonates. (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery".)

- Provide time for safe transport of the mother, if indicated, to a facility that has an appropriate level of neonatal care if she delivers preterm. In utero transport avoids the possibility that the mother and infant will be separated in the first few hours/days of life. (See "Inter-facility maternal transport".)

- Prolong pregnancy (when safe to do so) when underlying, self-limited conditions that can cause labor, such as pyelonephritis or abdominal surgery, are present but unlikely to cause recurrent preterm labor.

In addition, many providers administer tocolytics to women with recurrent preterm labor before 34 weeks in an attempt to prolong gestation, even when another course of corticosteroid therapy and/or maternal transfer is unnecessary. The value of this approach has not been studied in a randomized trial.

PATIENT SELECTION

General principles — Women in the early phases of acute preterm labor, when cervical dilation is not advanced, are optimum candidates for tocolytic therapy [4]. Tocolysis is indicated when the overall benefits of delaying delivery outweigh the risks, which need to be assessed on a case-by-case basis. In a practice bulletin, the American College of Obstetricians and Gynecologists (ACOG) opined: "Interventions to reduce the likelihood of delivery should be reserved for women with preterm labor at a gestational age at which a delay in delivery will provide benefit to the newborn. Because tocolytic therapy is generally effective for up to 48 hours, only women with fetuses that would benefit from a 48 hour delay in delivery should receive tocolytic treatment" [5].

Inhibition of acute preterm labor is less likely to be successful as labor advances to the point that cervical dilation is greater than 3 cm. Tocolysis can still be effective in these cases, especially when the goal is to administer antenatal corticosteroids or safely transport the mother to a tertiary care center [4-7]. (See 'Treatment goals' above.)

Lower and upper gestational age limits

- **Lower limit** – The minimum gestational age at which inhibition of preterm labor is a reasonable intervention is controversial, and largely based on expert opinion. The authors would give tocolytics to a woman less than 22 weeks of gestation if she has a self-limited condition that could cause an acute episode of preterm labor but is unlikely to cause recurrent preterm labor. As an example, we would attempt to inhibit contractions related to an appendectomy or acute pyelonephritis at 20 weeks of gestation in the absence of maternal sepsis [8,9].

  In the United States, a workshop comprised of obstetric and pediatric experts suggested 22+0 weeks as the lower limit for consideration of tocolysis if antenatal steroids were concurrently administered [10], given this gestational age is at the limit of viability and corticosteroid effectiveness. ACOG and the Society for Maternal-Fetal Medicine (SMFM) recommend not administering tocolysis before 24 weeks of gestation, but consider its use at 23 weeks based on individual circumstances [11]. (See "Periviable birth (limit of viability)" and "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery", section on 'Candidates for a first ACS course by gestational age'.)

- **Upper limit** – There is more consensus about the upper gestational age limit for treatment of preterm labor. We agree with ACOG and SMFM that 34 weeks of gestation defines the threshold at which perinatal morbidity and mortality are sufficiently low that the potential maternal and fetal complications and costs associated with inhibition of preterm labor and short-term delay of delivery are not justified [5,12].

Contraindications — Tocolysis is contraindicated when the maternal/fetal risks of prolonging pregnancy or the risks associated with these drugs are greater than the risks associated with preterm birth. Although the relative risks of pregnancy prolongation versus delivery need to be assessed on a case-by-case basis, established contraindications to labor inhibition include [5]:

- Intrauterine fetal demise
- Lethal fetal anomaly
- Nonreassuring fetal status
- Preeclampsia with severe features or eclampsia
- Maternal hemorrhage with hemodynamic instability
- Intraamniotic infection

- Preterm prelabor rupture of membranes, except in the absence of infection when needed for maternal transport, steroid administration, or both
- Medical contraindications to the tocolytic drug

Known or suspected fetal pulmonary maturity is not an absolute contraindication to tocolysis, as preterm birth is also associated with nonpulmonary morbidities.

Contraindications to use of specific drugs are reviewed below in the discussions of specific tocolytics.

INDICATIONS FOR EVALUATION OF AMNIOTIC FLUID FOR SUBCLINICAL INFECTION

There is no consensus as to whether women in acute preterm labor should be evaluated routinely for subclinical intraamniotic infection or the appropriate tests for this diagnosis.

- Before or just after administering first-line tocolysis, we obtain amniotic fluid via amniocentesis for gram stain and glucose level in patients who are afebrile but have nonspecific laboratory or physical findings suggestive of infection, such as leukocytosis, unexplained maternal or fetal tachycardia, or uterine tenderness. We culture the fluid for aerobes, anaerobes, *Ureaplasma* species, and *Mycoplasma* species.

  We would not begin/continue the first tocolytic if the amniotic fluid tests are suggestive of subclinical infection. Amniotic fluid cultures are positive in almost 65 percent of women in whom tocolysis with a single agent is not successful [13].

- For women who continue to contract after first-line therapy and have not been evaluated for subclinical infection, we perform amniocentesis for gram stain and glucose level before beginning a second-line tocolytic agent. We would not begin a second tocolytic if the amniotic fluid tests are suggestive of subclinical infection.

OUR APPROACH TO TREATMENT

We base our selection of tocolytic drug on efficacy and safety. In a 2012 network meta-analysis of 95 randomized trials of tocolytic therapy for preterm labor, all of the commonly used tocolytic agents (cyclooxygenase inhibitors, beta-agonists, calcium channel blockers, magnesium sulfate, oxytocin receptor antagonists) were statistically more effective than placebo/no tocolytic for delaying delivery for 48 hours [14]. Cyclooxygenase inhibitors (eg, indomethacin) and calcium channel blockers (eg, nifedipine) had the highest probability of being the best therapy for preterm labor on the basis of the four outcomes: delivery delayed by 48 hours, neonatal mortality, neonatal respiratory distress syndrome, and maternal side effects.

Choice of first-line therapy

- For most women at 24 to 32 weeks of gestation who are candidates for tocolysis, we use indomethacin for first-line therapy. Data from randomized trials suggest it is superior to placebo and has a favorable maternal and fetal side effect profile at this gestational age. We do not use indomethacin for more than 72 hours because of concern about premature constriction of the ductus arteriosus and oligohydramnios. Dosing, side effects, efficacy, and contraindications are described below. (See 'Cyclooxygenase inhibitors (eg, indomethacin)' below.)

  We use nifedipine as a first-line agent for women who have a contraindication to indomethacin therapy (maternal platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, or asthma [in women with hypersensitivity to aspirin]). Dosing, side effects, efficacy, and contraindications are described below. (See 'Calcium channel blockers (eg, nifedipine)' below.)

- For women at 32 to 34 weeks of gestation, we use nifedipine for first-line therapy, given the potential for adverse fetal effects with use of indomethacin at this gestational age. Dosing, side effects, efficacy, and contraindications are described below. (See 'Calcium channel blockers (eg, nifedipine)' below.)

Choice of second-line therapy — If the first-line drug does not inhibit contractions, we discontinue it and begin therapy with another agent. We avoid concurrent use of tocolytic drugs because of the increased risk of side effects and the absence of evidence of efficacy [15]. However, we selectively use combinations of tocolytics in very early gestations; the decision is made on a case-by-case basis.

- For most women at 24 to 32 weeks, we use nifedipine for second-line therapy. For those who received nifedipine as a first-line agent at 24 to 32 weeks, we switch to terbutaline. Dosing, side effects, efficacy, and contraindications are described below. (See 'Calcium channel blockers (eg, nifedipine)' below and 'Beta-agonists (eg, terbutaline)' below.)

- For women at 32 to 34 weeks, we use terbutaline for second-line therapy. Dosing, side effects, efficacy, and contraindications are described below. (See 'Beta-agonists (eg, terbutaline)' below.)

Duration of tocolysis — We discontinue tocolytics 48 hours after administration of the first corticosteroid dose. (See 'Efficacy' above.)

Retreatment — If a second episode of acute preterm labor occurs, our indications for retreatment are the same as for a primary episode (ie, delay delivery for corticosteroid administration [primary or rescue] and/or maternal transfer). There are no data on the role of repeated courses of tocolytics for treatment of recurrent preterm labor.

A single course of therapy does not delay delivery by weeks or months because tocolytics do not remove the underlying stimulus that initiated preterm labor (eg, subclinical intraamniotic infection, abruption, uterine overdistension) or reverse parturitional uterine changes (eg, cervical dilation and effacement). (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery", section on 'Use of rescue (salvage, booster) ACS'.)

MOST EFFECTIVE TOCOLYTIC DRUGS

Cyclooxygenase inhibitors (eg, indomethacin)

Mechanism of action — Cyclooxygenase (COX, or prostaglandin synthase) is the enzyme responsible for conversion of arachidonic acid to prostaglandins, which are critical in parturition. COX exists in two isoforms, COX-1 and COX-2. COX-1 is constitutively synthesized in gestational tissues, while COX-2 is inducible, dramatically increasing in the decidua and myometrium during term and preterm labor. Nonspecific COX inhibitors reduce prostaglandin production by inhibition of both COX-1 and 2; specific inhibitors are available for inhibition of COX-2 (eg, celecoxib) [16-20].

Efficacy — Indomethacin, a nonspecific COX inhibitor, is the most commonly used tocolytic of this class. In a 2015 meta-analysis of two randomized trials comparing indomethacin with placebo for treatment of preterm labor, use of indomethacin reduced the risk of delivery within 48 hours of initiation of treatment in both trials, but the confidence interval was wide (relative risk [RR] 0.20, 95% CI 0.03-1.28; two trials, n = 70) [21]. There was no clear increase in any adverse neonatal outcome. In comparative trials, indomethacin reduced the risk of birth within 48 hours of initiation of treatment compared with any beta-agonist (RR 0.27, 95% CI 0.08-0.96; two trials, n = 100) and appeared to be as effective as nifedipine (RR 1.08, 95% CI 0.58-2.01; two trials, n = 230).

There is limited information on the use of COX-2 inhibitors for treatment of preterm labor in humans [22-26]. Further evaluation of the safety and efficacy of COX-2 inhibitors for inhibition of preterm labor is warranted before introducing these drugs into clinical practice; however, most of these agents have either been withdrawn from the market or issued with boxed warnings regarding the risk of serious adverse events (discussed below).

Maternal side effects — Maternal side effects, including nausea, esophageal reflux, gastritis, and emesis, are seen in approximately 4 percent of women treated with indomethacin for preterm labor. Platelet dysfunction may

occur. Alterations in maternal cardiovascular physiology are minimal. (See "Nonselective NSAIDs: Overview of adverse effects".)

The gastrointestinal side effects of COX-2 inhibitors are less frequent and less severe than those associated with nonspecific COX inhibitors [27]. However, a boxed warning has been added to the labeling of COX-2 inhibitors because of excess adverse cardiovascular outcomes (eg, myocardial infarction, stroke). (See "Overview of COX-2 selective NSAIDs" and "NSAIDs: Adverse cardiovascular effects".)

Fetal side effects — The primary fetal concerns with use of indomethacin and other COX inhibitors (eg, sulindac, nimesulide) are constriction of the ductus arteriosus and oligohydramnios. Possible adverse neonatal effects are also a concern, but data are conflicting.

Constriction of the ductus arteriosus — Premature narrowing or closure of the ductus arteriosus can lead to pulmonary hypertension in the newborn and fetal and neonatal tricuspid regurgitation from increased right ventricle afterload. Several cases of premature ductal constriction have been reported in pregnancies in which the duration of indomethacin exposure exceeded 48 hours [28,29]; however, this complication has not occurred in more than 500 fetuses exposed to shorter durations of indomethacin treatment [30-32].

Ductal constriction appears to depend upon both gestational age and duration of exposure. It has been described in gestations as early as 24 weeks but is most common after 31 to 32 weeks [33]. Therefore, indomethacin is **not** recommended after 32 weeks of gestation (some guidelines advise against use after 28 or 30 weeks). Before 32 weeks, fetal echocardiographic evaluation is useful for monitoring ductal effects if the duration of therapy exceeds 48 hours. Sonographic signs of ductal narrowing include tricuspid regurgitation, right ventricular dysfunction [34], and pulsatility index less than 1.9 [35].

Oligohydramnios — Maternal administration of indomethacin and other COX inhibitors after 20 weeks of gestation reduces fetal urine production and, in turn, amniotic fluid volume, potentially leading to oligohydramnios. The mechanism is enhanced vasopressin action and reduced renal blood flow [36,37]. The greatest risk of oligohydramnios is with exposure >48 hours and particularly exposure for several days; amniotic fluid generally returns to normal within 24 to 48 hours of discontinuing the drug [24,38-40].

In one study of the use of indomethacin or ibuprofen for greater than 72 hours in 67 women with preterm labor, ultrasound-documented oligohydramnios was noted in 70 percent of patients treated with indomethacin and 27 percent of patients treated with ibuprofen, but in less than 3 percent of untreated controls [41]. One of the pregnancies in the control group was complicated by intrauterine growth restriction. By comparison, a study in which indomethacin was administered for 48 hours to patients with preterm labor and then serial sonograms were performed daily for seven days or until discharge reported that 2 of the 61 patients had oligohydramnios on the initial sonogram at 48 hours but the amniotic fluid index returned to normal in the next 24 hours after drug discontinuation [38].

Neonatal effects — Neonatal complications linked with in utero indomethacin exposure include bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus, periventricular leukomalacia, and intraventricular hemorrhage [42-46]. These associations are controversial. In a 2015 meta-analysis including 27 observational studies, there were no statistical differences in the rates of respiratory distress syndrome, patent ductus arteriosus, neonatal mortality, neonatal sepsis, bronchopulmonary dysplasia, or intraventricular hemorrhage (all grades) in exposed versus unexposed newborns [47]. However, increased risks were observed for severe intraventricular hemorrhage (grade III to IV RR 1.29, 95% CI 1.06-1.56), necrotizing enterocolitis (RR 1.36, 95% CI 1.08-1.71), and periventricular leukomalacia (RR 1.59, 95% CI 1.17-2.17). Exposures in the studies occurred at ≤28 weeks to <37 weeks of gestation. This meta-analysis was not able to analyze data by dose or duration of therapy or exposure during the second versus third trimester; therefore, the impact of these factors could not be evaluated.

Neonatal renal failure has been attributed to in utero exposure to nonsteroidal antiinflammatory drugs but causality has not been established; renal impairment in these cases could have been related to prematurity and other factors

[48].

Whether use of indomethacin has long-term developmental effects is also unclear [49-51]. Significant variations in study designs and small numbers of subjects preclude making a definitive conclusion about the safety or potential harm of indomethacin tocolysis.

Contraindications — Maternal contraindications to COX inhibitors include platelet dysfunction or bleeding diathesis, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma (in women with hypersensitivity to aspirin) [5]. (See "Nonselective NSAIDs: Overview of adverse effects" and "Overview of COX-2 selective NSAIDs".)

Dose — The dose of indomethacin for labor inhibition is 50 to 100 mg loading dose (may be given orally or per rectum), followed by 25 mg orally every four to six hours. Fetal blood concentrations are 50 percent of maternal values, but the half-life in the neonate is substantially longer than that in the mother (15.0 versus 2.2 hours).

Monitoring — If indomethacin is continued for longer than 48 hours, sonographic evaluation for oligohydramnios and narrowing of the fetal ductus arteriosus is warranted at least weekly [52,53]. Evidence of oligohydramnios or ductal constriction should prompt discontinuation of this therapy.

Calcium channel blockers (eg, nifedipine)

Mechanism of action — Calcium channel blockers directly block the influx of calcium ions through the cell membrane. They also inhibit release of intracellular calcium from the sarcoplasmic reticulum and increase calcium efflux from the cell. The resulting decrease in intracellular free calcium inhibits calcium-dependent myosin light-chain kinase phosphorylation, leading to myometrial relaxation. (See "Physiology of parturition at term".)

Efficacy — Most trials of calcium channel blockers for inhibition of acute preterm labor have used nifedipine. In a 2014 meta-analysis of randomized trials of calcium channel blockers compared with placebo/no treatment for preterm labor, use of a calcium channel blocker reduced the risk of delivery within 48 hours (RR 0.30, 95% CI 0.21-0.43; two trials, n = 173 participants), but there was no statistical reduction in this outcome compared with other classes of tocolytics (eg, compared with beta-agonists: RR 0.86, 95% CI 0.67-1.10; 19 trials, n = 1505 women) [54]. However, calcium channel blockers showed statistical benefits over beta-agonists with respect to prolongation of pregnancy (mean difference 4.38 days, 95% CI 0.25-8.52), serious neonatal morbidities (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, jaundice), and maternal adverse effects (RR 0.36, 95% CI 0.24-0.53).

The relative safety, maternal tolerance, ease of administration, and reduction in adverse neonatal outcomes support use of nifedipine rather than beta-agonists for inhibition of acute preterm labor. The available beta-agonist comparative trials have used ritodrine, which was often excessively dosed during intravenous therapy and inadequately dosed during oral therapy. The poor methodologic quality of these trials limits their clinical utility and the value of meta-analysis.

Maternal side effects — Nifedipine is a peripheral vasodilator; thus, it may cause symptoms such as nausea, flushing, headache, dizziness, and palpitations. Arterial relaxation results in decreased total vascular resistance, which is accompanied by a compensatory rise in cardiac output (reflex increase in heart rate and increased stroke volume). These compensatory changes generally maintain blood pressure in women who have no underlying myocardial dysfunction [55]; however, severe hypotension has been described in case reports [56,57]. By comparison, beta-agonists are more frequently associated with adverse cardiovascular changes [58-60]. (See "Major side effects and safety of calcium channel blockers".)

Fetal side effects — Doppler studies of human fetal systemic, umbilical, and uteroplacental blood flow have been reassuring [55,61-63]. The fetal acid-base status in the umbilical cord at delivery and from percutaneously obtained blood sampling has not provided convincing evidence of fetal hypoxia or acidosis when these agents were used.

These findings were based upon studies using 10 mg sublingual dosing of nifedipine. There are no data regarding fetal side effects with the oral doses commonly used for labor inhibition.

Contraindications — Calcium channel blockers are contraindicated in women with known hypersensitivity to the drugs, hypotension, or preload-dependent cardiac lesions and should be used with caution in women with heart failure with reduced ejection fraction.

The concomitant use of a calcium-channel blocker and magnesium sulfate could act synergistically to suppress muscular contractility, which could result in respiratory depression [64].

Dose — An optimal nifedipine dosing regimen for treatment of preterm labor has not been established. A common approach is to administer an initial loading dose of 20 to 30 mg orally, followed by an additional 10 to 20 mg orally every 3 to 8 hours for up to 48 hours, with a maximum dose of 180 mg/day. In a meta-analysis including 26 trials, nifedipine dosing regimens included loading doses of 10 to 30 mg, followed by 10 to 20 mg every 4 to 8 hours for 24 to 72 hours; 12 studies repeated a loading dose every 15 to 20 minutes to a maximum of 40 mg during the first hour of treatment if contractions persisted [65].

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.

Beta-agonists (eg, terbutaline) — The beta-2-agonists ritodrine and terbutaline have been studied in several randomized, placebo-controlled trials. Salbutamol and hexoprenaline have also been evaluated, but data are sparse [66]. Although ritodrine is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of preterm labor, it is no longer available in the United States.

Mechanism of action — The beta-2 receptor agonists cause myometrial relaxation by binding with beta-2-adrenergic receptors and increasing intracellular adenyl cyclase. An increase in intracellular cyclic adenosine monophosphate activates protein kinase and results in the phosphorylation of intracellular proteins. The resultant drop in intracellular free calcium interferes with the activity of myosin light-chain kinase. Interference with myosin light-chain kinase inhibits the interaction between actin and myosin; thus, myometrial contractility is diminished. However, target cells eventually become desensitized to the effect of beta-agonists, thereby decreasing efficacy with prolonged use [67,68]. The reduction in response over time is known as tachyphylaxis.

Efficacy — The efficacy of beta-agonist therapy for tocolysis has been evaluated in multiple trials; most used ritodrine.

In a 2014 meta-analysis of randomized, placebo-controlled trials of beta-agonists for inhibiting preterm labor, use of beta-agonists decreased the number of women giving birth within 48 hours (RR 0.68, 95% CI 0.53-0.88; 10 trials, 1209 women) and within seven days (RR 0.80, 95% CI 0.65-0.98; five trials, 911 women), but not before 37 weeks of gestation (RR 0.95, 95% CI 0.88-1.03; 10 trials, 1212 women) [69]. There was a trend toward reduction in respiratory distress syndrome (RR 0.87, 95% CI 0.71-1.08; eight trials, 1239 infants) but no effect on the neonatal death rate (RR 0.90, 95% CI 0.27-3.00; six trials, 1174 infants).

These trends, with the upper limit of the confidence interval just crossing the threshold of no effect, suggest that relative risk reductions of up to 30 percent in respiratory distress syndrome are plausible, and may be demonstrated by trials with a larger total sample size, improved identification of patients with true preterm labor, and exclusion of pregnancies over 34 weeks of gestation. A limitation of many of the trials included in the meta-analysis is that antenatal corticosteroids were not routinely administered. Thus, the neonatal benefits of delaying delivery for 48 hours were not fully realized.

Comparative data versus calcium channel blockers are discussed above. (See 'Calcium channel blockers (eg, nifedipine)' above.)

Maternal side effects — Many of the maternal side effects of beta-agonists are related to stimulation of beta-1 adrenergic receptors, which increase maternal heart rate and stroke volume, and stimulation of beta-2-adrenergic receptors, which causes peripheral vasodilation, diastolic hypotension, and bronchial relaxation. The combination of these two cardiovascular effects leads to tachycardia, palpitations, and lower blood pressure.

In placebo-controlled randomized trials, common symptoms associated with use of beta-agonists included tremor (39 versus 4 percent with placebo), palpitations (18 versus 4 percent), shortness of breath (15 versus 1 percent), and chest discomfort (10 versus 1 percent) [70].

Pulmonary edema is uncommon, occurring in 0.3 percent of patients [71,72]. Pulmonary edema probably results from several additive factors including fluid overload from excessive intravenous crystalloid infusion, decreased time for diastolic filling time due to increased heart rate, and the increased plasma volume of pregnancy. Alternatively, pulmonary edema may be unrelated to the beta-agonist therapy and instead may be due to increased vascular permeability related to infection, inflammation, or preeclampsia [72,73]. (See "Acute respiratory failure during pregnancy and the peripartum period", section on 'Pulmonary edema'.)

Beta-agonists also have clinically important metabolic effects, including hypokalemia (39 versus 6 percent with placebo), hyperglycemia (30 versus 10 percent with placebo), and lipolysis [70]. Myocardial ischemia is a rare complication.

Fetal side effects — Beta-agonists cross the placenta. Fetal effects, such as fetal tachycardia, are analogous to the maternal effects noted above. Neonatal hypoglycemia may result from fetal hyperinsulinemia in response to prolonged maternal hyperglycemia. Fetal acid/base status and neonatal well-being are not compromised by these agents [74].

The relationship between in utero exposure to beta-agonists for tocolysis and neonatal intraventricular hemorrhage (IVH) is controversial. Most studies have concluded that beta-agonist use decreased or did not affect the risk of IVH [75-77], while some suggested an increase in risk [78,79]. All of the studies were retrospective and therefore suffer from potential bias, particularly since so many other intrapartum interventions might have impacted neonatal outcome.

Contraindications — Labor inhibition with a beta-2-agonist is relatively contraindicated in women with tachycardia-sensitive cardiac disease, because of the potent chronotropic effects of these drugs, and in women with poorly controlled hyperthyroidism or diabetes mellitus [5]. Well-controlled diabetes mellitus is not a contraindication to beta-agonist therapy, as long as glucose and potassium concentrations are closely monitored and maintained in the normal range. In most women with diabetes, hourly blood glucose monitoring and an intravenous insulin drip are required to maintain euglycemia.

Beta-agonists should be used with caution in women at risk for massive hemorrhage (such as women with placenta previa or abruption) since the resultant cardiovascular effects (tachycardia, hypotension) may interfere with the mother's ability to respond to ongoing hemorrhage, and may confuse the clinical presentation.

In the United States, the FDA has warned that injectable terbutaline should not be used in pregnant women for prolonged (beyond 48 to 72 hours) treatment of preterm labor or prevention of recurrent preterm labor because of the potential for serious maternal heart problems and death [80]. The FDA also opined that oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns.

For treatment of acute preterm labor, however, the health care professional may decide that the benefit of terbutaline injection for an individual patient in a hospital setting clearly outweighs the risk. For example, a short course of injectable terbutaline is a reasonable option for inhibition of acute preterm labor or for management of tetanic uterine contractions or tachysystole with an abnormal fetal heart rate pattern in labor.

Dose — Data are too limited to support the use of any particular beta-agonist over another. In the United States, terbutaline is the most commonly used beta-agonist for labor inhibition and has a preferential effect on beta-2-adrenergic receptors. It is often given subcutaneously by intermittent injection. The dose is variable: 0.25 mg can be administered subcutaneously every 20 to 30 minutes for up to four doses or until tocolysis is achieved. Once labor is inhibited, 0.25 mg can be administered subcutaneously every three to four hours until the uterus is quiescent for 24 hours.

Terbutaline can also be administered as a continuous intravenous infusion. We suggest starting the infusion at 2.5 to 5 mcg/min and increasing by 2.5 to 5 mcg/min every 20 to 30 minutes to a maximum of 25 mcg/min, or until the contractions have abated. At this point, the infusion is reduced by decrements of 2.5 to 5 mcg/min to the lowest dose that maintains uterine quiescence.

As discussed above (see 'Contraindications' above), the FDA concluded that the risk of serious adverse events outweighs any potential benefit to pregnant women receiving prolonged treatment with terbutaline (beyond 48 to 72 hours) [81].

Monitoring — During beta-agonist administration, the clinician should monitor cumulative fluid intake, urine output, and maternal symptoms, especially shortness of breath, chest pain, or tachycardia. We suggest withholding the drug if the maternal heart rate exceeds 120 beats/min.

Glucose and potassium concentrations should be monitored every four to six hours during parenteral drug administration, since hyperglycemia and hypokalemia commonly occur. Significant hypokalemia should be treated to minimize risk of arrhythmias. Significant hyperglycemia can be treated with insulin.

LESS EFFECTIVE TOCOLYTIC DRUGS

Oxytocin receptor antagonists (eg, atosiban)

Mechanism of action — Atosiban is a selective oxytocin-vasopressin receptor antagonist. Although commonly used in Europe and elsewhere, it is not available in the United States. In normal parturition, oxytocin stimulates contractions by inducing conversion of phosphatidylinositol to inositol triphosphate, which binds to a protein in the sarcoplasmic reticulum causing release of calcium into the cytoplasm. Oxytocin receptor antagonists compete with oxytocin for binding to oxytocin receptors in the myometrium and decidua, thus preventing the increase in intracellular free calcium that occurs when oxytocin binds to its receptor [82,83]. These drugs also inhibit oxytocin-induced production of prostaglandin F2alpha, but not prostaglandin E2 [82,84,85]. Theoretically, atosiban should be more effective at later gestational ages since oxytocin receptor concentration and uterine responsiveness to oxytocin increase with advancing gestation.

Efficacy — In a 2014 meta-analysis of randomized trials comparing the oxytocin receptor antagonists (atosiban, barusiban) versus placebo for inhibition of preterm labor, use of these drugs did **not** reduce the risk of birth within 48 hours of initiation of treatment (relative risk [RR] 1.05, 95% CI 0.15-7.43; two trials, 152 women), the risk of preterm birth at less than 28 weeks of gestation (RR 3.11, 95% CI 1.02-9.51; one trial, 501 women), or the risk of preterm birth at less than 37 weeks (RR 1.17, 95% CI 0.99-1.37; two trials, 664 women) [86]. All neonatal morbidity and mortality outcomes evaluated were statistically similar in both groups.

In the absence of a demonstration of efficacy in placebo-controlled trials, it is difficult to interpret active-control trials. This difficulty is compounded by the fact that trials using the beta-2-agonists terbutaline and salbutamol as the active-control used controls that have not been proven to be effective. With these limitations, the same meta-analysis found that atosiban was as effective as beta-agonists for preventing preterm birth within 48 hours of initiating treatment (RR 0.89, 95% CI 0.66-1.22) [86]. Use of atosiban was associated with a significantly lower risk of maternal side effects requiring cessation of treatment than beta-agonists (RR 0.05, 95% CI 0.02-0.11), which is the drug's major advantage. A subsequent trial (APOSTEL III) randomly assigned 510 women with threatened preterm

labor to receive oral nifedipine or intravenous atosiban for 48 hours and found that the drugs resulted in similar composite perinatal outcomes and a similar proportion of pregnancies that did not deliver within 48 hours [87].

The US Food and Drug Administration (FDA) declined to approve the use of atosiban for tocolysis because of concerns about the drug's safety when used in pregnancies less than 28 weeks of gestation (see below) [88]. It is available for clinical use in Europe.

Maternal side effects — The main side effects associated with use of atosiban are hypersensitivity and injection site reactions. Adverse maternal cardiovascular effects have not been reported [89,90]. The overall frequency of side effects in women given atosiban is significantly less than that reported for any other drug used for inhibition of preterm labor [70,91]. Atosiban may compete with antidiuretic hormone in the kidney based on incomplete receptor specificity for oxytocin receptor; however, no clinical sequelae related to this mechanism have been reported.

Fetal side effects — Atosiban crosses the placenta; fetal levels are approximately 12 percent of maternal levels. The drug has not been proven to cause neonatal cardiovascular or acid/base alterations [90,92]. However, one trial showed a trend toward a higher rate of fetal-infant death in patients taking atosiban [89]. These fetal-infant deaths were associated with infection and extreme prematurity, although a relationship to atosiban cannot be excluded. Randomization in this trial was not stratified by gestational age and led to an imbalance such that most of the very preterm infants (less than 26 weeks of gestation) were assigned to the atosiban group. Therefore, the mortality difference may be attributable to the lower gestational age of newborns in this group.

A small cohort study reported similar rates of death and/or intraventricular hemorrhage for infants delivered at 24 to 31 weeks of gestation and exposed to atosiban versus calcium channel blockers in utero, and exposure to either tocolytic was associated with a lower rate of the composite outcome than no tocolytic exposure [93].

Contraindications — There are no absolute contraindications to use of atosiban.

Dose — Atosiban is administered intravenously beginning with a bolus of 6.75 mg followed by a 300 mcg/min infusion for three hours, and then 100 mcg/min for up to 45 hours [94]. Initial and terminal half-lives are 13 and 102 minutes, respectively.

Magnesium sulfate

Mechanism of action — The precise mechanism of magnesium's effects on uterine contractions has not been completely elucidated, despite more than 40 years of study. Magnesium probably competes with calcium at the level of the plasma membrane voltage-gated channels. It hyperpolarizes the plasma membrane and inhibits myosin light-chain kinase activity by competing with intracellular calcium at this site. Interference with the activity of myosin light-chain kinase reduces myometrial contractility [95-97]. (See "Physiology of parturition at term".)

Efficacy — In a 2014 meta-analysis of randomized trials comparing magnesium sulfate with no treatment/placebo control, magnesium sulfate administration did **not** result in a statistical reduction in birth <48 hours after trial entry (RR 0.56, 95% CI 0.27-1.14; three trials, 182 women) or improvement in neonatal and maternal outcomes [98]. Antenatal corticosteroids were not routinely administered.

In 33 comparative trials, magnesium sulfate was neither more nor less effective than other tocolytics (betamimetics, calcium channel blockers, cyclooxygenase inhibitors, prostaglandin inhibitors, or human chorionic gonadotropin) [98]. These comparative trials must be interpreted with caution since they were not designed as equivalence trials, and thus are inadequately powered to evaluate the equivalence of magnesium sulfate to other tocolytics. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine consider magnesium sulfate an option for short-term prolongation of pregnancy (up to 48 hours) to allow administration of antenatal corticosteroids to pregnant women at risk for preterm delivery within 7 days [12].

Maternal and fetal side effects — Magnesium sulfate causes fewer minor maternal side effects than beta-agonists, but the risk of major adverse risk events is comparable [99]. Diaphoresis and flushing are the most

common side effects; magnesium toxicity is related to serum concentration. Maternal therapy causes a slight decrease in baseline fetal heart rate and fetal heart rate variability, which are not clinically important. Antenatal fetal assessment test results (eg, biophysical profile score and nonstress test reactivity) are not significantly altered. (See "Preeclampsia: Management and prognosis", section on 'Regimen' and "Preeclampsia: Management and prognosis", section on 'Signs of magnesium toxicity'.)

Retrospective epidemiologic studies have reported a significant increase in radiographic bone abnormalities in neonates with in utero exposure to magnesium sulfate for more than seven days, and a significant difference in the serum values of magnesium, calcium, phosphorus, and osteocalcin (a marker of bone formation) at birth between neonates unexposed to magnesium sulfate and those who were exposed [100,101]. There is some evidence that these effects are transient [102]. Based on these and other data, in 2013, the FDA advised health care professionals in the United States against using magnesium sulfate infusions for more than five to seven days to stop preterm labor [103]. We agree with this recommendation, given the potential for adverse fetal effects and because tocolytic therapy is generally effective for only up to 48 hours. ACOG suggests limiting magnesium sulfate therapy to 48 hours in women between 24 and 34 weeks of gestation with preterm labor [12].

Neuroprotective effects — Predelivery administration of magnesium sulfate is neuroprotective for the neonate. The minimum duration of administration that results in neuroprotection is not known but is less than 24 hours. Neuroprotection is discussed in detail separately. (See "Neuroprotective effects of in utero exposure to magnesium sulfate".)

If tocolysis is indicated because of persistent preterm labor in a patient receiving magnesium sulfate for neuroprotection, the most effective tocolytic with the most favorable side-effect profile should be used.

Contraindications — Magnesium sulfate tocolysis is contraindicated in women with myasthenia gravis. (See "Management of myasthenia gravis in pregnancy", section on 'Complications'.)

Magnesium sulfate should also be avoided in women with known myocardial compromise or cardiac conduction defects because of its anti-inotropic effects.

Magnesium is eliminated by the kidneys. Thus, women with impaired renal function will have an exaggerated rise in serum magnesium and may develop magnesium toxicity at the usual doses of administration so the maintenance dose should be reduced or eliminated.

The concomitant use of a calcium channel blocker and magnesium sulfate could act synergistically to suppress muscular contractility, which could result in respiratory depression [64].

Dose — Magnesium sulfate is usually administered as a 6 gram intravenous load over 20 minutes, followed by a continuous infusion of 2 g/hour [104]. The infusion rate is titrated based upon assessment of contraction frequency and maternal toxicity. The optimum regimen has not been determined [105]. Higher maternal weight increases the time required to reach steady state levels [106].

Since magnesium sulfate is excreted by the kidneys, dosing should be adjusted in women with renal insufficiency (defined as a serum creatinine greater than 1.0 mg/dL [88.4 micromol/L]) or an alternative drug should be used. If magnesium sulfate is given, such women should receive a standard loading dose (since their volume of distribution is not altered), but a reduced maintenance dose (1 gram per hour or no maintenance dose if the serum creatinine is greater than 2.5 mg/dL [221 micromol/L]) with close monitoring of the serum magnesium concentration every six hours.

Women with renal insufficiency 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. The urine output and deep tendon reflexes should be closely monitored. Magnesium levels may be useful in monitoring women on maintenance magnesium therapy who have

concomitant renal disease. (See "Hypermagnesemia: Causes, symptoms, and treatment", section on 'Symptoms of hypermagnesemia'.)

Monitoring — In women with normal renal function, signs and symptoms of magnesium toxicity can be assessed by history and physical examinations. Routine magnesium levels are not necessary.

If life-threatening symptoms of magnesium toxicity occur (cardiac or respiratory compromise), calcium gluconate (1 gram intravenously over 5 to 10 minutes) is an effective counteractive therapy but should not be used to treat mild symptoms.

Nitric oxide donors (eg, nitroglycerin)

Mechanism of action — Nitric oxide (NO) is produced in a variety of cells and is essential for maintenance of normal smooth muscle tone. NO is synthesized during the oxidation of L-arginine (an essential amino acid) to L-citrulline, which then diffuses from the generator cell. This reaction is catalyzed by the enzyme nitric oxide synthase (NOS). The interaction between NO and soluble guanylyl cyclase (sGC), which is present in nearby effector cells, represents a widespread signal transduction mechanism that couples diverse extracellular stimuli of NO formation to the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP) in target cells. The increase in cGMP content in smooth muscle cells activates myosin light chain kinases leading to smooth muscle relaxation [107].

Efficacy — In a 2014 meta-analysis of randomized trials that compared nitroglycerin by any route with placebo (three trails), beta-adrenergic receptor agonists (nine trials), and nifedipine (one trial), use of nitroglycerin did **not** significantly prolong pregnancy by ≥48 hours, reduce preterm birth, or result in improved neonatal outcomes compared with any of the comparators [108]. However, the studies were underpowered to identify differences between groups for most outcomes.

Maternal side effects — NO donors cause dilation of arterial smooth muscle, which commonly causes headache and might result in maternal hypotension. Although maternal hypotension could compromise uterine and placental blood flow, adverse neonatal effects have not been reported when these drugs were used for inhibition of preterm labor. Other side effects are similar to those of the calcium channel blockers: dizziness, flushing, and palpitations.

Contraindications — NO donors should not be used in women with hypotension or with preload-dependent cardiac lesions, such as aortic insufficiency.

Dose — NO donors may be administered via transdermal patches or intravenously; the optimum dose has not been determined. In general, the drug dose and interval should be titrated to cessation of contractions, while maintaining an adequate blood pressure. Two options are:

- 10 mg nitroglycerin patch applied to the skin of the abdomen. After one hour, if there is no reduction in contraction frequency or intensity, an additional patch is applied; no more than two patches are administered simultaneously. The patches can be left in place for 24 hours, after which they are removed and the patient reassessed [109].
- An intravenous infusion rate of 20 mcg/min until contractions stop [110].

INEFFECTIVE APPROACHES

Antibiotic therapy — Although subclinical genital tract infection clearly contributes to the pathogenesis of preterm birth, there is no evidence-based role for antibiotic therapy in the prevention of prematurity in patients with acute preterm labor.

A 2013 meta-analysis evaluated the use of antibiotics as an adjunct to tocolysis for inhibiting preterm labor up to 36 weeks of gestation in women with intact membranes [111]. Women allocated to receive antibiotics and those allocated to no antibiotics had similar rates of delivery within 48 hours or seven days of initiating treatment, preterm

birth less than 36 or 37 weeks, perinatal mortality, respiratory distress syndrome, neonatal sepsis, and other measures of neonatal morbidity. Maternal infection, however, was significantly reduced in the antibiotic group (chorioamnionitis or endometritis relative risk 0.74, 95% CI 0.63-0.86). Although 14 trials involving almost 8000 women were included in the analysis, it was dominated by one large trial that administered broad spectrum antibiotics orally [112].

The lack of benefit from antibiotics may be because the subclinical infectious process leading to preterm labor may be too advanced for treatment to be effective by the time preterm labor is clinically apparent. It is also possible that once the inflammatory cascade has been triggered, it will continue to amplify whether or not the inciting infection is treated. However, clinicians should be cautious before concluding there are no benefits from antibiotic therapy of preterm labor. Theoretically, a subgroup of women who have subclinical intrauterine infection may benefit from treatment with antibiotics, as demonstrated in a primate model [113].

Antibiotics for prevention of early-onset group B streptococcal disease, for prolonging latency in preterm prelabor rupture of membranes, and for treatment of clinical chorioamnionitis are discussed separately. (See "Early-onset neonatal group B streptococcal disease: Prevention" and "Preterm prelabor rupture of membranes: Clinical manifestations and diagnosis" and "Intraamniotic infection (clinical chorioamnionitis or triple I)".)

Progesterone supplementation — Women in acute preterm labor do not benefit from progesterone supplementation. A full discussion of the use of progesterone to prevent preterm birth can be found separately. (See "Progesterone supplementation to reduce the risk of spontaneous preterm labor and birth", section on 'Threatened or established preterm labor'.)

Bedrest, hydration, and sedation — There is no convincing evidence that bedrest, hydration, or sedation is effective for prevention or treatment of preterm labor [114-116]. Furthermore, extended and hospitalized bedrest increase the risk of thromboembolic events [117,118].

MANAGEMENT AFTER CESSATION OF CONTRACTIONS

The management of pregnant women in whom preterm contractions resolve is discussed separately. Maintenance tocolytic therapy is ineffective. (See "Management of pregnancy after resolution of an episode of acute idiopathic preterm labor".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Preterm labor and birth".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Preterm labor (The Basics)")
- Beyond the Basics topics (see "Patient education: Preterm labor (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- For women with preterm labor <34 weeks of gestation, we suggest tocolytic therapy (**Grade 2B**). A delay in delivery for 48 hours for administration of antenatal steroids can provide benefit to the newborn. (See 'Patient selection' above and "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery".)
- The goal of treatment is to delay delivery so that antenatal corticosteroids can be administered and achieve their maximal effect; allow safe transport of the mother, if indicated, to a facility that can provide an appropriate level of neonatal care if the patient delivers preterm; and prolong pregnancy when there are underlying, self-limited causes of labor, such as abdominal surgery, that are unlikely to cause recurrent preterm labor. Treatment can be discontinued after these goals have been achieved. (See 'Treatment goals' above.)
- For women 24 to 32 weeks of gestation who are candidates for tocolysis, we suggest indomethacin as first-line therapy for labor inhibition (**Grade 2B**). It appears to be superior to placebo and has a relatively favorable maternal and fetal side effect profile and is compatible with concomitant neuroprotective administration of magnesium sulfate. (See 'Our approach to treatment' above.)

  Contraindications to indomethacin use include maternal platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, or asthma (in women with hypersensitivity to aspirin). We avoid the use of indomethacin in gestations over 32 weeks and caution against their use for more than 72 hours because of concern about premature narrowing or closure of the ductus arteriosus. (See 'Cyclooxygenase inhibitors (eg, indomethacin)' above.)

  We suggest nifedipine for women at 24 to 32 weeks who have a contraindication to indomethacin (**Grade 2B**). (See 'Our approach to treatment' above.)
- For women 32 to 34 weeks of gestation who are candidates for tocolysis, we suggest nifedipine as the first-line therapy (**Grade 2B**). (See 'Our approach to treatment' above.)
- If the first-line drug does not inhibit contractions, we discontinue it and begin therapy with another agent. For second-line therapy, we use nifedipine at 24 to 32 weeks, and terbutaline at 32 to 34 weeks and for patients at 24 to 32 weeks who received nifedipine as a first-line agent. We avoid concurrent use of tocolytic drugs because of the increased risk of side effects and the absence of evidence of efficacy. (See 'Our approach to treatment' above.)
- In women with an acute episode of preterm labor, bedrest, hydration, sedatives, antibiotics, and progesterone supplementation are ineffective for preventing preterm birth. (See 'Ineffective approaches' above.)

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