A Review of Systemic Opioids Commonly Used for Labor Pain Relief

Deborah Anderson, CNM, MSN

Parenteral opioids for pain relief during labor have been the subject of research for many decades. Commonly used systemic opioids provide limited pain relief during labor yet are used extensively for managing labor pain. These opioids share similar pharmacologic profiles but differ in potency, pharmacokinetics, and side effects. This article reviews the pharmacokinetics, pharmacodynamics, and clinical research related to the commonly used systemic labor pain analgesics morphine, meperidine, fentanyl, remifentanil, butorphanol, and nalbuphine.


Keywords: butorphanol, fentanyl, labor pain, meperidine, morphine, nalbuphine, opioids, pharmacology, remifentanil

INTRODUCTION

Systemic opioids are widely used for providing labor analgesia,1 yet patterns of intrapartum opioid use are unclear. A 2001 survey2 of 378 obstetric units in the United States found that 34% to 42% of parturients received parenteral drugs for labor pain. Parenteral opioids commonly used in the United States have been reported to include meperidine (Demerol), morphine, fentanyl (Sublimaze), butorphanol (Stadol), and nalbuphine (Nubain), although no recent surveys have been published to verify this.3,4 Recent surveys of intrapartum analgesia in the United Kingdom3 and Norway4 reported that pethidine (another generic name for meperidine that is more commonly used in Europe) is still the opioid most commonly used during labor (43% and 77% of obstetric units, respectively), with intramuscular administration being the most common route. In the United Kingdom,3 49% of the units surveyed offered patient-controlled analgesia (PCA), with the most common drug being remifentanil (Ultiva), followed by morphine and fentanyl. Similarly, in Belgian labor and delivery units, 36% of those surveyed used opioid PCA administration, with remifentanil being the most common (77%) patient-controlled drug used.5

This article reviews the pharmacokinetics, pharmacodynamics, and clinical research related to commonly used systemic labor pain analgesics. Morphine, meperidine, fentanyl, remifentanil, butorphanol, and nalbuphine are addressed.

BACKGROUND

The fundamental principles underlying management of opioid use for labor pain are individualization of care and the balancing of pain relief with maternal, fetal, and neonatal safety. The optimal labor opioid has a rapid onset and offset of action; rapid metabolism and elimination; and minimal undesired maternal, fetal, and neonatal side effects. The analgesic should not affect the woman’s ability to participate in labor and birth.

When women choose opioids for labor pain relief, counseling regarding medication options includes maternal, fetal, and neonatal risks and benefits; unknown short-term and long-term risks; type of opioids available in a particular setting; optimal timing of dosing; realistic expectations of analgesia results and their limitations; and review of alternatives. Understanding each woman’s plan for pain relief measures includes knowing whether she prefers to initiate a request for analgesia rather than being offered opioids, because offering analgesia may inadvertently undermine a woman’s plan for a labor without analgesia.

Strategies used for the selection of a safe systemic labor pain analgesic center around an opioid’s efficacy for pain relief; side effect profile; and maternal, fetal, and neonatal safety. When managing opioid dosing, it is important to keep in mind that women vary highly in their physiologic responses to opioids. They also vary in their perceptions of the degree to which pain must be reduced to be meaningful. Continuation of a supportive presence and nonpharmacologic methods of pain relief should accompany the provision of opioids.

To minimize neonatal effects, opioid analgesics are used primarily in the active phase of labor. Following opioid administration, close supervision of the woman and newborn for unwanted side effects and having oxygen and naloxone (Narcan) available are important safety considerations. Additional lactation support for establishing breastfeeding may be helpful for women who have received opioids during labor.

OVERVIEW OF OPIOIDS

The pharmacologic differences and characterization of opioids are the result of their interactions with opioid receptors. Opioid receptors located throughout the central nervous system and peripheral tissues are part of an endogenous pain-relieving system that includes the production of naturally occurring opioid peptides (eg, enkephalins, endorphins, dynorphins) or ligands. These naturally occurring morphine-like ligands as well as exogenous opioid ligands (eg, morphine, fentanyl) bind specifically and reversibly to opioid receptors and activate a response. There are 3 different types of opioid receptors: mu, kappa, and/or delta.6

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The Agonist Versus Antagonist Response

The subsequent biologic response and pharmacologic difference of the opioid ligand-receptor complex depends on which opioid receptor the drug binds to and whether the opioid ligand functions as agonist, antagonist, or mixed agonist-antagonist. An agonist is a molecule that combines with 1 or more receptors to trigger a physiologic reaction. An antagonist is a molecule that binds to a cell receptor without eliciting a biologic response and blocks binding by agonists. Agonist-antagonists initiate mixed reactions because of an agonist effect at 1 receptor type and an antagonist effect at a different receptor type. The response of the ligand-receptor complex also is differentiated by the strength of interaction between a ligand and its receptor (affinity) and the strength of the effect of the response (efficacy).6

Most clinically relevant opioids are mu agonists and have their primary activity at mu receptors. Mu receptors mediate analgesia, sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, decreased gastrointestinal motility, and urinary retention. Kappa receptors are responsible for sedation, dyspnea, dysphoria, spinal analgesia, and dependence. The effects of delta receptors are not well studied but may be related to psychomimetic and dysphoric effects.6 Morphine and fentanyl have a high affinity for mu receptors and are potent analgesics. Meperidine, in contrast, is a relatively weak mu and delta agonist. Butorphanol is an example of an agonist-antagonist and acts as a kappa receptor agonist and a mu receptor antagonist. Naloxone, an opioid antagonist, binds to each of the 3 receptors and has its highest affinity for the mu opioid receptor.7

Opioids commonly used for treating labor pain share similar pharmacologic profiles but differ in receptor relationships, potency, pharmacokinetics (eg, elimination half-life, metabolism), analgesic effect, and side effects. In addition, an individual's opioid sensitivity varies and is determined by genetic variation in the mu opioid receptor and differences in metabolism related to age, sex, genetic make-up, renal function, and concurrent use of medications.6

The Effect of Pharmacogenomics

The rapidly progressing field of pharmacogenomics, the study of an individual's genetic make-up and response to a drug, offers insight into why individuals have different clinical responses to the same dose of an opioid. Genetic variations, or polymorphisms, within genes encoding mu opioid receptors, metabolic enzymes, and transport proteins affect an individual's response to opioid medications. The most commonly identified polymorphism (G118) in the gene encoding the mu opioid receptor (OPRM1) has been linked to the variability of the analgesic effect of morphine. Individuals with G118 polymorphism have a reduced or variable response to morphine and increased opioid dose requirements during opioid therapy.8

Polymorphisms within genes encoding metabolic enzymes may contribute to either diminished, absent, or excessive metabolism of an opioid, leading to differences in drug effectiveness and altered risk for adverse drug effects. Codeine, for example, is metabolized to the active metabolite, morphine, by the enzyme CYP2D6. This metabo-
Table 1. Significant Drug-Drug Interactions of Systemic Opioids Used for Labor Analgesia

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>All†</td>
<td>Alcohol</td>
<td>Increased CNS depressant effect of alcohol</td>
</tr>
<tr>
<td>All</td>
<td>Amphetamines</td>
<td>Increased analgesic effect of opioid</td>
</tr>
<tr>
<td>All</td>
<td>Phenothiazines</td>
<td>Increased hypotensive effect of opioid; some increase in respiratory-depressant effects, sedation, and/or analgesic effect</td>
</tr>
<tr>
<td>All</td>
<td>Antihistamines</td>
<td>Potentiates sedation and respiratory depression</td>
</tr>
<tr>
<td>All</td>
<td>CNS depressants (eg, barbiturates)</td>
<td>Potentiates sedation and respiratory depression</td>
</tr>
<tr>
<td>All</td>
<td>Cimetidine (Tagamet)</td>
<td>Inhibits opioid metabolism; increased CNS toxicity</td>
</tr>
<tr>
<td>All</td>
<td>Erythromycin</td>
<td>Increased opioid effects</td>
</tr>
<tr>
<td>All</td>
<td>SSRIs</td>
<td>Increased serotonergic effect of SSRI; may cause serotonin syndrome</td>
</tr>
<tr>
<td>Meperidine, fentanyl</td>
<td>MAOIs</td>
<td>Increased orthostatic hypotension</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Ketoconazole (Nizoral),</td>
<td>CYP34A inhibitor; increases fentanyl blood levels</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Itraconazole (Sporanox)</td>
<td>CYP34A inhibitor; increases fentanyl blood levels</td>
</tr>
<tr>
<td>Remifentanil, fentanyl</td>
<td>Selected HIV retrovirals³</td>
<td>Increased bradycardic and hypotensive effect</td>
</tr>
<tr>
<td>Remifentanil, fentanyl</td>
<td>Beta blockers</td>
<td>Increased bradycardic and hypotensive effect</td>
</tr>
<tr>
<td>All</td>
<td>Antihypertensives</td>
<td>Increased orthostatic hypotension</td>
</tr>
<tr>
<td>All</td>
<td>Herbs: valerian, St. John’s wort, kava kava, gotu kola</td>
<td>May increase CNS depression</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.

†Morphine, meperidine (Demerol), fentanyl (Sublimaze), remifentanil (Ultrab), butorphanol (Stadol), nalbuphine (Nubain).

Drug-drug interactions of retrovirals are beyond the scope of this article. Prescribers should consult comprehensive pharmacology references for information about specific retrovirals.

nausea and vomiting, dizziness, altered mental status, euphoria, decreased gastric mobility, decreased gastric emptying, and urinary retention. Sedation may result in less maternal mobility and time in upright positions. This in turn can affect a parturient’s pain perception. An altered mental status may also affect a parturient’s ability to engage in decision making.

Fetal effects include a temporary decrease in fetal heart rate variability or a pseudosinusoidal fetal heart rate pattern. This may result in additional interventions such as continuous electronic fetal heart rate monitoring. In the neonate, opioids may cause respiratory depression and subtle neurobehavioral changes.

The effects of opioids on breastfeeding behaviors have not been adequately studied. Riordan et al14 has postulated:

When present at concentrations below that needed to induce respiratory depression, opioids may exert other, more subtle, effects on the central nervous system, including neurobehavioral effects. Without optimal muscle tone and reflexes, the neonate is unlikely to suckle correctly, causing trauma, soreness, and pain, which will deter all but the most determined women.

Epidemiologic studies have found an association between intrapartum fetal exposure to opiates and opiate addiction later in life.15–17 In a 2000 case-control study17 of individuals who were followed from the prenatal period through 18 to 27 years of age, investigators compared labor pain analgesia and other obstetric variables in 69 drug-abusing men and women with 33 non-abusing siblings. They observed that 3 or more doses of meperidine, phenobarbital (Luminal), and/or secobarbital (Seconal) given within 10 hours before birth was associated with a 4.7 times greater odds ratio for drug addiction later in life (95% confidence interval [CI], 1.0-44.1).

MORPHINE

Morphine was first isolated in 1806 and named morphium for the god of sleep. It was introduced as a labor pain medication in the late 1800s but was soon abandoned because of concerns related to neonatal depression. Its intrapartum use reappeared in the early 1900s as a component of twilight sleep, a combination of morphine and scopolamine. Combining scopolamine with morphine allowed for reduced amounts of morphine to be used; however, this drug combination produced confusion, amnesia, little analgesic effect, and neonatal respiratory depression.18 After the 1920s, providers gradually increased the amounts of morphine and began to combine twilight sleep with other forms of anesthesia.19 Despite its undesirable effects, use of twilight sleep continued for many years. After meperidine was introduced as an intrapartum analgesic in the 1940s, and subsequent studies indicated that morphine was associated with a higher risk
<table>
<thead>
<tr>
<th>Drug (Brand name)</th>
<th>Usual Dose</th>
<th>Onset (Minutes)</th>
<th>Peak Effects (Minutes)</th>
<th>Duration of Action</th>
<th>Elimination Half-life</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active metabolite of morphine: M6G</td>
<td>IV: 2-5 mg/4 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV: 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV: 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV: 1-3 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Adults: 2 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Faster absorption when administered in deltoid muscle compared with gluteal muscle</td>
</tr>
<tr>
<td></td>
<td>IM: 10 mg/4 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IM: 10-20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IM: 0.5-1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IM: 3-5 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal: 43 min&lt;sup&gt;c&lt;/sup&gt; Neonates: 6.5 ± 2.8 h&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Use lower doses with patients with impaired ventilation or asthma</td>
</tr>
<tr>
<td>Meperidine or pethidine (Demerol)</td>
<td>IV: 25-50 mg/1-2 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV: 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV: 5</td>
<td>IM, IV: 2-4 h</td>
<td>Maternal: 3-7 h Neonates: 18-23 h</td>
<td>Fetal exposure highest 1-4 h after maternal administration, with associated neonatal respiratory depression; highest 2-3 h after administration</td>
</tr>
<tr>
<td>Active metabolite of meperidine: normeperidine</td>
<td>IM: 50-100 mg/2-4 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IM: 10-20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IM: 30-60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IM: 2-5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal: 21 h Neonates: 63 h</td>
<td>May temporarily decrease FHR variability</td>
</tr>
<tr>
<td>Fentanyl (Sublimaze)</td>
<td>IV: 50-100 mcg/1 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV: 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV: 5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV: 30-60 min</td>
<td>Adults: 3-4 h&lt;sup&gt;a&lt;/sup&gt; Neonates: 75-440 min</td>
<td>When administered as an infusion, context sensitive decrement time (the time to a 50% reduction in blood concentration after cessation of a steady infusion) increases; With higher doses or prolonged infusions, fentanyl becomes longer acting&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>IM: 50-100 mcg/1 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IM: 7-15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IM: 10-20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IM: 1-2 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Transient decreased FHR variability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maximum cumulative labor dose is usually 500-600 mcg</td>
</tr>
</tbody>
</table>
Table 2. Pharmacokinetic Profiles of Selected Opioids

<table>
<thead>
<tr>
<th>Drug (Brand name)</th>
<th>Usual Dose</th>
<th>Onset (Minutes)</th>
<th>Peak Effects (Minutes)</th>
<th>Duration of Action</th>
<th>Elimination Half-life</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remifentanil (Ultiva)</td>
<td>PCA administration with varying dosing</td>
<td>0.5–1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2&lt;sup&gt;f&lt;/sup&gt;</td>
<td>20 min&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Adults: 9 min&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Potent maternal respiratory depressant Dose at beginning of uterine contraction</td>
</tr>
<tr>
<td>Butorphanol (Stadol)</td>
<td>IV: 1-2 mg q 3-4 h&lt;sup&gt;a&lt;/sup&gt; IM: 1-2 mg q 3-4 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV: 2-3 IM: 10-20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV: 5-10 IM: 30-60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV or IM: 4-6 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Adults: 2.5-3.5 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal ceiling effect on respiratory depression and analgesia Fetal transient pseudosinusoidal FHR pattern May precipitate acute withdrawal syndrome in an opiate-dependent mother and neonate</td>
</tr>
<tr>
<td>Nalbuphine (Nubain)</td>
<td>IV or IM: 10 mg/3 h&lt;sup&gt;a&lt;/sup&gt; IM: &lt;15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV: 2-3&lt;sup&gt;a&lt;/sup&gt; IM: 30-60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV: 30 IM: 30-60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV: 2-4 h IM: 4-6 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Adults: 2-5 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal ceiling effect on respiratory depression and analgesia at 30 mg May precipitate acute withdrawal syndrome in an opiate-dependent mother and neonate</td>
</tr>
</tbody>
</table>

Abbreviations: FHR, fetal heart rate; IM, intramuscular; IV, intravenous; M6G, morphine-6-glucuronide; PCA, patient-controlled analgesia.

<sup>a</sup>ACOG<sup>75</sup>  
<sup>b</sup>Baumann<sup>76</sup>  
<sup>c</sup>Gerdin et al<sup>23</sup>  
<sup>d</sup>Kart et al<sup>25</sup>  
<sup>e</sup>Gustein et al<sup>69</sup>  
<sup>f</sup>Hinova et al<sup>64</sup></td>

Efficacy and Side Effects of Morphine

Side effects and adverse effects of morphine include euphoria, altered mental status, respiratory depression, nausea and vomiting, decreased intestinal motility and constipation, urinary retention, flushing of skin, urticaria, orthostatic hypotension, and decreased fetal heart rate variability. Morphine and its metabolite morphine-3-glucuronide accumulate in colostrum and breast milk and are excreted in breast milk in small amounts.<sup>26</sup>

In recent years, a small (<i>N = 20</i>), prospective, randomized, double-blind study<sup>27</sup> comparing intravenous morphine (mean 12.4 mg, range 3.8-14.4 mg) to intravenous pethidine (mean 108 mg, range 90-132 mg) as labor analgesia found no significant analgesic effect following administration of either medication. Women in both groups equally reported sedation after dosing, and sedative scores increased with each repeated dose. There was no change in strength of uterine contractions as measured with intrauterine pressure catheters. The rate of nausea was significantly higher in the pethidine group (6/10 vs 1/10, <i>P</i> < 0.03), although differences in rates of emesis were not statistically significant. There was no correlation between dose and Apgar scores and no neonatal respiratory depression necessitating treatment. The median time between the end of opioid administration and birth was 6.3 hours (range 1.0-15.5 hours). The authors concluded that labor pain is not sensitive to intravenous morphine or pethidine and that the primary effect of intrapartum use of these drugs is heavy sedation.
Effect of Morphine on Labor

There have been no published, randomized clinical trials addressing the effect of morphine on labor.

Clinical Considerations

Although systemic morphine is sometimes used for labor analgesia,  morphine is most often administered in the subarachnoid space as a part of regional anesthesia or in the epidural space for postoperative pain relief. Additionally, it is used for therapeutic rest in the treatment of prolonged latent phase of labor. Morphine doses for therapeutic rest recommended by Friedman are 15 mg subcutaneously or intramuscularly. An additional 10 mg may be considered 20 minutes later if contractions continue and there is no respiratory depression. After morphine administration, 85% of women will benefit from 6 to 10 hours of rest and awake in active labor, 10% will stop having contractions, and 5% will continue with the same contraction pattern. Hydroxyzine (Vistaril) 25 mg to 50 mg intramuscularly can be administered along with morphine to potentiate its analgesic effect and prevent nausea. Hydroxyzine additionally has an anxiolytic effect. Promethazine (Phenergan) 25 mg to 50 mg may be administered with morphine to prevent emesis; it also has a sedative effect.

Further studies are needed to evaluate the effectiveness and adverse effects of morphine as labor analgesia and to further understand the effect of its active metabolite on the newborn.

MEPERIDINE/PETHIDINE

In the 1940s, meperidine began to replace morphine for labor pain analgesia and has since become the most widely used systemic labor medication. This popularity may in part be related to familiarity, low cost, and studies that were performed more than 30 years ago that concluded that meperidine was associated with a lower risk of respiratory depression than morphine. Its use in obstetrics has become increasingly controversial because of its undesirable effects on the woman and neonate.

Meperidine is a relatively weak synthetic mu agonist that binds to both mu and kappa opioid receptors. It is estimated to have 10% of the effectiveness of morphine. Promethazine 25 mg to 50 mg may be used in combination with meperidine to reduce nausea and provide a sedative effect.

Efficacy and Side Effects of Meperidine

Investigations of meperidine's intrapartum analgesic efficacy have varied in their conclusions. Some authors have found meperidine to provide little to no labor pain relief. In contrast, when compared with a placebo, investigators found a modest but significant (P = .01) reduction in visual analogue pain scores with 100 mg of intramuscular meperidine. Common maternal side effects include sedation and nausea and vomiting. A temporary decrease in fetal heart rate variability also is associated with meperidine use during labor.

The woman, fetus, and newborn metabolize meperidine in the liver to the active metabolite normeperidine, which can produce analgesia and central nervous system stimulation in adults or depression and neurobehavioral changes in neonates. Meperidine and normeperidine cross the placenta and have long half-lives in women and neonates (Table 2). The birth of a newborn between 1 and 4 hours following meperidine administration is associated with neonatal respiratory depression, with maximal respiratory depression occurring between 2 and 3 hours after administration. Additionally, with multiple doses of meperidine, both meperidine and normeperidine accumulate in maternal plasma and in fetal tissues; therefore, a newborn whose mother received multiple injections of meperidine may have high normeperidine levels at birth. Further, because of the lengthy elimination half-life of normeperidine, long drug-to-delivery intervals may result in high levels of maternal and fetal normeperidine, which may put neonates at risk for neurobehavioral depression. Most importantly, these metabolite-related adverse effects cannot be reversed with naloxone.

Two trials have compared the effect of a single dose of 100 mg of meperidine with placebo on newborn outcomes. With a mean drug-to-delivery interval of 2 hours, investigators found that meperidine was associated with a 4-fold increase in the number of 1-minute Apgar scores of less than 7 (RR, 4.11; 95% CI, 1.72-9.8) and significantly more 5-minute Apgar scores of less than 7 (RR, 11.82; CI, 0.66-210.25). Other investigators demonstrated that with a mean drug-to-delivery interval of 5.3 hours, there was no significant difference between the meperidine and placebo group in the number of 1-minute and 5-minute Apgar scores of less than 7, umbilical artery pH, and admissions to neonatal intensive care units.

Effect of Meperidine on Labor

Most studies have found no effect of meperidine on labor outcomes. In a randomized controlled trial, Sosa et al investigated the effect of meperidine on the length of labor in parturients with a diagnosis of dystocia during the active phase of labor. Four hundred and seven parturients were randomized to receive 100 mg of intravenous meperidine or a placebo. There were no significant differences between groups in duration of labor or route of birth. There were, however, significantly more women in the meperidine group who required oxytocin augmentation (RR 2.24; 95% CI, 1.13-4.43). When meperidine was compared with other opioids, no difference in duration of labor, oxytocin use, cesarean birth, or route of birth was demonstrated.

Effect of Meperidine on Breastfeeding

Meperidine and its metabolites accumulate in colostrum and breast milk and may be associated with newborn neurobehavioral alterations and unfavorable effects on developing breastfeeding behaviors. Wittels et al conducted a perspective, randomized study of breastfeeding women who underwent cesarean births and compared intravenous PCA administration of meperidine to intravenous PCA administration of morphine. Meperidine was associated with significantly more neurobehavioral depression in breastfeeding newborns on the third and fourth days of life when compared with the
behavior of the newborns in the morphine cohort ($P < .05$), despite similar overall doses of morphine and meperidine.26,43

Nissen et al44 demonstrated that newborns of parturients who received 100 mg of intramuscular pethidine administered between 1.1 and 5.3 hours before birth had depressed newborn sucking behavior ($P < .05$) and delayed initiation of lip and mouth movement (22 minutes vs 11 minutes; $P = .01$) when compared with newborns who were exposed to meperidine 8.1 to 9.9 hours before birth.

Clinical Considerations
Because neonatal adverse effects are related to dose-delivery interval, timing of meperidine administration becomes important. Ideally, to reduce the risk of neonatal respiratory depression, meperidine is not given when birth is anticipated within 1 to 4 hours after administration. Because multiple dose regimens may result in maximum fetal accumulation of both meperidine and normeperidine, with associated newborn depression, single doses of meperidine during labor are preferable to multiple doses.38

In summary, meperidine’s well-documented adverse effects in the neonate, effect on breastfeeding behaviors, active metabolite, and slow clearance do not support any advantage to its use during labor. Other short-acting opioids with rapid onset and offset and no active metabolites may be preferred.

FENTANYL
Fentanyl citrate, a synthetic opioid derivative of meperidine, was first synthesized in the 1950s and was initially used as an intravenous anesthetic. Studies of intravenous fentanyl use during labor first appeared in the literature in 1989.45 It is now used in many labor and delivery units for labor pain relief.

A potent opioid agonist, fentanyl interacts primarily with mu receptors. It has a greater analgesic potency than morphine, with 100 mcg of fentanyl equivalent in analgesic effect to 10 mg of morphine. Fentanyl is metabolized in the liver by CYP34A to the inactive and nontoxic metabolites hydroxy fentanyl, norfentanyl, and despropionyl fentanyl.46 Fentanyl is eliminated in urine and stool and by the lungs.47

Efficacy and Side Effects of Fentanyl
Rapidly crossing the blood-brain barrier, fentanyl produces analgesia, sedation, and may cause respiratory depression, nausea, and vomiting. Because it is highly lipophilic, fentanyl rapidly crosses the placenta. In animal studies (sheep) it is present in the fetal blood within 1 minute and its level peaks at 5 minutes after maternal intravenous administration.48 Fetal exposure to fentanyl is associated with temporary depressant effects such as fewer body movements between contractions, less overall time moving, and temporary abolishment of breathing movements at 10 minutes after dosing.49 Short-term fetal heart rate variability between uterine contractions is reduced for approximately 30 minutes following administration.45,49,50

Although fentanyl may be administered by other routes, published studies regarding use for intrapartum parenteral analgesia have assessed only intermittent intravenous bolus administration and PCA administration (Table 3).

Rayburn et al45 compared parturients who received intravenous fentanyl for labor pain to women who did not receive analgesia or anesthesia during labor and determined that at low doses of intravenous fentanyl, laboring women experienced temporary analgesia and sedation with no immediate risks to them and their newborns.

When intravenous fentanyl was compared with intravenous meperidine for labor pain relief in a randomized, nonblinded trial ($N = 105$ women with uncomplicated pregnancies at term in active labor), both fentanyl and meperidine produced similar reduction in pain scores; however, fentanyl was associated with less sedation, nausea, and vomiting and fewer newborns requiring naloxone therapy (1/49 vs 7/56, respectively; $P < .05$). There was no difference in rates of decreased fetal heart rate variability, Apgar scores, and neonatal neurologic and adaptive capacity scores. Because fentanyl had fewer maternal and newborn side effects, the investigators suggested that fentanyl might be preferable to meperidine for labor analgesia.33

When fentanyl and butorphanol were compared, butorphanol was found to provide better pain relief in the early stages of active phase labor ($P < .05$), yet both drugs reduced pain scores only slightly during the latter part of first-stage labor (cervical dilation 7-9 cm). Rates of maternal sedation, nausea, and vomiting were found to be similar as well as frequency of decreased fetal heart rate variability persisting beyond 30 minutes, Apgar scores, neonatal neurologic and adaptive capacity scores, naloxone therapy, and umbilical cord gas values. The authors concluded that although rates of maternal and neonatal side effects were comparable, butorphanol might be preferable to fentanyl for pain relief in early active labor.50

Effect of Fentanyl on Labor
Studies of the effect of intermittent intravenous bolus administration of fentanyl on labor outcomes have had inconsistent findings. When compared with women who did not receive analgesia or anesthesia during labor, women who received intravenous fentanyl were more likely to have oxytocin augmentation and a longer active phase of labor.45 In contrast, the clinical trials that compared intravenous fentanyl to intravenous meperidine, butorphanol, or PCA fentanyl demonstrated no difference in contraction frequency or duration,50 oxytocin augmentation,33,50 length of labor,33 or route of birth.33,50

Patient-controlled Administration of Fentanyl
Low doses of intravenous bolus fentanyl (cumulative dose 161.6 mcg ± 109.2 mcg) also have been compared with equivalent doses of PCA fentanyl and were found to have no clinical advantage over intravenous bolus administration.51

High doses of PCA fentanyl have been compared with epidural anesthesia and have demonstrated varying results. Nikkola et al52 found that although epidural anesthesia was more effective for pain relief than PCA fentanyl (cumulative dose range 190 mcg-885 mcg) during active labor, overall satisfaction with analgesia did not differ between groups.
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<tr>
<th>Authors of Study</th>
<th>Study Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
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<tr>
<td>Rayburn et al45</td>
<td>Prospective nonrandomized controlled trial</td>
<td>137 parturients in active labor</td>
<td><strong>Experimental:</strong> IV bolus of fentanyl 50-100 mcg/h. Mean (SD) cumulative fentanyl dose 140 mcg/h (42 mcg) ranging 50-600 mcg. Two-thirds of group received ≤ 100 mcg total dose, and 90% received &lt; 300 mcg. <strong>Control:</strong> No analgesia or anesthesia</td>
<td><strong>Maternal:</strong> Fentanyl group with temporary analgesia, mild sedation, mood modification, temporary relief of fears, relaxation, drowsiness. <strong>Fetal:</strong> 30 min of decreased variability. <strong>Labor:</strong> Fentanyl group had higher rate of oxytocin augmentation ($P &lt; .0001$) and longer active phase labors ($P &lt; .001$). No difference in route of birth. <strong>Newborn:</strong> No differences in frequencies of newborn depressed respirations, low Apgar scores, or neurologic and adaptive capacity scoring at 2-4 h and 24 h following birth.</td>
</tr>
<tr>
<td>Rayburn et al33</td>
<td>Prospective randomized controlled trial</td>
<td>105 parturients in active labor</td>
<td><strong>Experimental:</strong> IV bolus of fentanyl 50-100 mcg/h <strong>Control:</strong> IV bolus of meperidine (Demerol) 25-50 mg/h</td>
<td><strong>Maternal:</strong> VAS pain scores were not significantly different between groups. Pain scores improved only slightly between 8-10 cm and more so at 4-7 cm cervical dilation. Nausea, vomiting, and prolonged sedation less common in the women in the fentanyl group ($P &lt; .05$). <strong>Fetal:</strong> FHR variability not statistically different between groups. <strong>Labor:</strong> No significant differences in duration of labor, oxytocin use, cesarean birth. <strong>Newborn:</strong> Significantly fewer neonates required naloxone in the fentanyl group (2% vs 13%; $P &lt; .05$). No difference in Apgar scores, umbilical artery pH, or neurologic and adaptive capacity scoring at 2-4 h and 24 h postnatally.</td>
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<td>Atkinson et al50</td>
<td>Prospective randomized double-blind, controlled trial</td>
<td>100 parturients in active labor</td>
<td><strong>Experimental:</strong> IV bolus of fentanyl 50-100 mcg/h, limit 5 doses. <strong>Control:</strong> IV bolus of butorphanol (Stadol) 1-2 mg every 1-2 h, limit 5 doses</td>
<td><strong>Maternal:</strong> Significantly greater reduction in VAS pain scores at 15 and 60 min following initial dose of butorphanol ($P &lt; 0.05$) compared with fentanyl. At 7-9 cm cervical dilation, pain scores increased and both drugs reduced pain scores only slightly at 15 min after dosing. Mothers in fentanyl group requested more doses ($P &lt; .05$) and had more requests for epidural ($P &lt; .05$). Rates of nausea, vomiting, prolonged sedation, and decreased respiratory rate were similar.</td>
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<tr>
<th>Authors of Study</th>
<th>Study Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
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<tr>
<td>Rayburn et al(^{52})</td>
<td>Prospective randomized controlled trial</td>
<td>80 parturients in active labor</td>
<td>Experimental: PCA fentanyl 50 mcg loading dose, 10 mcg/h baseline, 10 mcg demand dose; lockout interval 12 min; Maximum hourly dose 60 mcg Cumulative dose used: 149.0 mcg (62.2 mcg), range 70-305 mcg</td>
<td>Fetal: No difference in temporary decrease in FHR variability and pseudosinusoidal pattern. Labor: No difference in contraction frequency or duration, oxytocin augmentation, or cesarean birth. Newborn: No difference in Apgar scores, cord gas values, naloxone use, or neuroadaptive scoring. Maternal: No difference in pain scores, sedation scores.</td>
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<tr>
<td>Nikkola et al(^{52})</td>
<td>Randomized controlled trial</td>
<td>20 parturients in active labor</td>
<td>Experimental: IV PCA fentanyl Loading dose 50 mcg fentanyl, 20 mcg demand dose; lockout interval 5 min; maximum dose 240 mcg/h Cumulative dose range 190 and 885 mcg, mean 447 (202 mcg) Control: epidural (bupivacaine 0.5%)</td>
<td>Maternal: Epidural provided significantly better pain relief ((P = .01)) per VAS pain score. Six of 10 mothers rated effectiveness of fentanyl as good to excellent; 8 of 10 rated epidural effectiveness as good to excellent. Satisfaction with analgesia did not differ significantly between groups. Mothers in fentanyl group had significantly more tiredness and dizziness ((P = .001)). No difference in rates of nausea and vomiting. Fetal: No difference in FHR variability 1 h after medication. Labor: No difference in labor duration. Newborn: No difference in Apgar scores, umbilical pH, or neurologic and adaptive capacity scoring at 1 and 13 h. During the first 12 h of life, minimum and maximum SpO(_2) values were significantly lower in the infants in the fentanyl group. SpO(_2) &lt; 90% was more common with fentanyl group ((P = &lt; .001); no infants required O(_2). Episodes of desaturation &lt; 80% did not differ between groups. No neonates required naloxone.</td>
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\(^{52}\) Reference numbers in the text are incorrect or missing. For a complete list of references, please refer to the original publication.
Women who received PCA fentanyl were more likely to have dizziness and tiredness. There was no difference between groups in nausea, vomiting, labor duration, Apgar scores, and neonatal neurologic and adaptive capacity scores. No newborns received naloxone. During the first 12 hours of life, minimum and maximum oxygen saturation values were significantly lower in the newborns in the fentanyl group. An oxygen saturation with pulse oximetry (SpO2) of less than 90% also was more common with newborns in the fentanyl group, although none of the newborns required oxygen supplementation. Because newborn desaturation events occurred during the first 12 hours of life, the authors recommended monitoring SpO2 for several hours after birth in newborns whose mothers receive the reported doses of PCA fentanyl. Conversely, Halpern et al53 found that pain relief and satisfaction with analgesia scores were better in the women receiving epidural anesthesia (bupivacaine plus fentanyl) when compared with parturients receiving PCA fentanyl (cumulative dose 350 mcg-1625 mcg). There was no difference between groups in route of birth, umbilical cord gas values, or 5-minute Apgar scores, although a longer second stage of labor was associated with epidural use. Women in the intravenous fentanyl group experienced more sedation and lower 1-minute Apgar scores. Active resuscitation was required in 52% of the neonates of women who received the studied doses of PCA fentanyl, compared with 31% in the epidural group. At the high doses studied, a large number of neonates required naloxone therapy (17% of the neonates in the PCA fentanyl group, 3% in the epidural group).

### Effect of Fentanyl on Breastfeeding

A small amount of fentanyl transfers into human milk following analgesic dosing. Women who received 50 mcg to 400 mcg of fentanyl intravenously during labor were found to have a very small amount of fentanyl in their breast milk.54 In another study,46 fentanyl was detected in colostrum in very small amounts following intravenous fentanyl analgesic dosing (126 mcg-189 mcg) during cesarean birth or postpartum tubal ligation. Highest concentrations in colostrum were at 45 minutes after intravenous administration, and fentanyl was undetectable at 10 hours after administration. Because of the small amount of fentanyl in colostrum, the small amount of colostrum initially consumed, the low bioavailability of fentanyl, and rapid decline in colostrum with time, the amount of fentanyl transferred to the neonate via colostrum is very low.

### Clinical Considerations

To date, 1 study has investigated the effect of mu opioid polymorphisms on the effect of labor analgesia. Landau et al55 demonstrated that parturients with the mu opioid receptor 304G variant required lower doses (P < .001) of intrathecal fentanyl to achieve labor pain relief. Although the effect of the 304G variant on a parturient’s response to intravenous fentanyl during labor has not been studied, other trials have found that intravenous morphine analgesia in nonpregnant patients with this variant increased, rather than decreased, morphine requirements. It is suggested that individual differences in analgesic response to route of

### Table 3. Summary of Comparative Investigations of Fentanyl (Sublimaze) for Labor Pain Relief

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<th>Authors of Study</th>
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<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
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<tr>
<td>Halpern et al53</td>
<td>Prospective randomized</td>
<td>242 parturients in active labor and second stage labor</td>
<td><strong>Experimental:</strong> Patient controlled epidural (0.08% bupivacaine and fentanyl 1.6 mcg/mL) Mean cumulative epidural fentanyl dose 200 mcg (range 132-244 mcg) <strong>Control:</strong> IV PCA fentanyl. Loading dose 100 mcg, then 50 mcg as needed until adequate pain relief. Followed by 25-50 mcg PCA demand dose; lockout interval 10 min. Lockout and demand dose could be increased or decreased by anesthesiologist. Total dose used: mean cumulative dose of 940 mcg (range 350-1625 mcg)</td>
<td><strong>Maternal:</strong> Epidural group with significantly greater reductions in VAS pain scores (P &lt; .001) and higher satisfaction scores (P = .02). Also, less antiemetic therapy (P = .01) and lower sedation scores (P &lt; .001). <strong>Fetal:</strong> Not evaluated. <strong>Labor:</strong> Epidural was associated with significantly longer second stage labor (P = .02). No difference in incidence of maternal fever, spontaneous vaginal births, assisted vaginal births, or cesarean births. <strong>Newborn:</strong> No difference in 5-min Apgar scores, umbilical artery gas values, or neonatal fever. More neonates in fentanyl group required active resuscitation (P = .001), naloxone (17% vs 3%; P = .001), and had lower 1-min Apgar scores.</td>
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Abbreviations: FHR, fetal heart rate; IV, intravenous; PCA, patient-controlled analgesia; SpO2, oxygen saturation with pulse oximetry; VAS, visual analogue scale.
administration in persons with this polymorphism may be related to a difference in spinal and systemic opioid pharmacokinetics.\textsuperscript{54} Currently, genotyping is not part of standard care; therefore, practitioners do not know whether parturients have variants that could affect analgesia sensitivity. Starting with low doses of opioids and titrating to a safe dose allows for individual variation in response.

Fentanyl’s rapid onset, short half-life, and lack of active metabolite make it a suitable choice for labor analgesia. Most commonly administered by intravenous bolus or PCA devices, lower doses of fentanyl provide modest amounts of pain relief with minimal adverse effects. Higher doses are associated with limited pain relief but with more maternal sedation and newborn respiratory depression. Even high doses lack effectiveness in the latter part of active labor.

**REMIFENTANIL**

Remifentanil use during labor was first reported in the late 1990s as an adjunct to general anesthesia for cesarean births.\textsuperscript{56} Since that time, various labor analgesia dosing regimens and their effect on laboring women and neonates have been studied.\textsuperscript{42,56–59} Remifentanil, like fentanyl, is in the anilidopiperidine class of synthetic opioids. It is an ultra short–acting synthetic mu opioid receptor agonist characterized by rapid onset of action and rapid offset.\textsuperscript{59} Because of its rapid offset, remifentanil is administered via intravenous PCA at the beginning of a uterine contraction and is likely to provide its peak effect with the next contraction. Remifentanil has a half-life of 4 minutes, metabolizes to the inactive metabolite remifentanil acid, and is virtually gone within 3 half-lives or 9 to 10 minutes after initial administration.

**Efficacy and Side Effects of Remifentanil**

Remifentanil results in temporary reduction in labor pain scores; pain reduction is dose related.\textsuperscript{58,60,61} Undesirable side effects include sedation, respiratory depression, and nausea and vomiting (range 0%-60%). Many studies of this opioid have reported periods of maternal desaturation during labor that have required oxygen supplementation.\textsuperscript{58–60,62}

Remifentanil rapidly crosses the placenta and is quickly metabolized and redistributed in the fetus.\textsuperscript{56} The fetal side effects may include temporary decreased fetal heart rate variability.\textsuperscript{63} There have been no reports of associated low Apgar scores or need for naloxone therapy.

Several randomized controlled trials have addressed unique dosing regimens and have demonstrated varying effects on pain scores and side effects (Table 4). When a fixed dose of PCA remifentanil was compared with PCA pethidine, Blair et al\textsuperscript{41} found no significant difference in reduction of pain relief scores during a 2-hour observation period but found satisfaction scores to be higher in the remifentanil group. Sedation scores increased over time in both groups. There was no significant difference in fetal heart rate baseline, Apgar scores, umbilical cord arterial pH values, naloxone use, or neonatal neurologic and adaptive capacity scores at 2 hours after birth. Neonatal neurologic and adaptive capacity scores were higher with remifentanil at 30 minutes after birth. The authors concluded that the doses of remifentanil studied resulted in no better pain scores than pethidine and that differing dose regimens may provide better pain relief.

In contrast, Thurlow et al\textsuperscript{60} found that PCA remifentanil provided better pain relief compared with intramuscular meperidine during the same-length observation period. Satisfaction scores were higher with remifentanil. Both groups experienced comparable rates of nausea and vomiting or minimum PO\textsubscript{2} saturation rates and comparable Apgar scores. The authors concluded that remifentanil is an acceptable alternative to meperidine, but because of its potential for respiratory depression, it must be administered with adequate supervision of the parturient. The authors also emphasized the importance of timing the remifentanil bolus dose at the start of contractions rather than when the contraction becomes painful to receive maximum pain relief and minimize side effects.

Evron et al\textsuperscript{63} compared increasing weight-based doses of PCA remifentanil to intramuscular meperidine and found better pain relief scores in the remifentanil group 2 hours after administration and better satisfaction scores 24 hours after birth. Remifentanil was associated with less sedation, less nausea and vomiting, and fewer desaturation events. Decreased fetal heart rate variability occurred less frequently with remifentanil. There were no differences in Apgar scores or umbilical cord arterial pH values. Rates of breastfeeding difficulties were not significantly different between groups (remifentanil 6.3%, meperidine 12.8%). The authors concluded that the intermittent incremental regimen of remifentanil studied provided better pain relief and had fewer side effects than meperidine.

Finally, when PCA remifentanil was compared with PCA meperidine or fentanyl, all pain scores initially improved, but remifentanil produced greater improvement than meperidine and fentanyl at 1 hour after administration. Three hours after opioid exposure, pain scores were not significantly different from the baseline in all groups. Sedation increased in all groups and was greatest with remifentanil. Desaturation events were more common with remifentanil and fentanyl compared with meperidine. Overall satisfaction scores were highest with remifentanil. There was no difference in neonatal outcomes. The authors concluded that, at the doses studied, remifentanil provided more pain relief than meperidine and fentanyl for a short time only and was associated with more sedation and respiratory depression.\textsuperscript{62}

**Effect of Remifentanil on Labor**

Studies of the effect of remifentanil on labor outcomes have had inconsistent findings. Women who received remifentanil had no difference in rates of oxytocin use\textsuperscript{42,63} or length of labor.\textsuperscript{41,42,63} One study\textsuperscript{60} found more operative vaginal births associated with remifentanil when compared with meperidine; another\textsuperscript{63} found no difference. When remifentanil was compared with fentanyl, remifentanil was associated with more operative births.\textsuperscript{62}

**Effect of Remifentanil on Breastfeeding**

The effect of remifentanil on breastfeeding has not been adequately studied. Only 1 study\textsuperscript{63} has addressed breastfeeding
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<tr>
<th>Author</th>
<th>Design</th>
<th>Interventions</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td><strong>Blair et al</strong>&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Double-blind, randomized controlled trial</td>
<td><strong>Experimental:</strong> PCA remifentanil 40 mcg/dose, 2 min lockout interval</td>
<td>Maternal: No difference between groups in reduction of VAS pain scores during 2 h observation. Overall maternal satisfaction higher (&lt;em&gt;P&lt;/em&gt; = .001) with remifentanil. No difference between groups in nausea, anxiety, or maternal desaturation less than 94% or 90%. Sedation increased over time and was similar between groups.</td>
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<td><strong>Control:</strong> PCA meperidine (Demerol) 15 mg/dose, 10 min lockout interval</td>
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<td>Total doses not available</td>
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<td>Nitrous oxide option available to both groups</td>
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<td><strong>Evron et al</strong>&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Double-blind, randomized controlled trial</td>
<td><strong>Experimental:</strong> Increasing doses of PCA remifentanil, 0.27-0.93 mcg/kg/bolus, maximum 1500 mcg/h. Mean total dose/h 270 mcg/kg</td>
<td>Maternal: Remifentanil associated with lower (&lt;em&gt;P&lt;/em&gt; &lt; .001) VAS pain scores at 1 h after initiation of medication and end of first stage labor and higher (&lt;em&gt;P&lt;/em&gt; &lt; .001) patient satisfaction scores 24 h after birth. Remifentanil also associated with less (&lt;em&gt;P&lt;/em&gt; &lt; .001) sedative effect, fewer (&lt;em&gt;P&lt;/em&gt; &lt; .007) desaturation events &lt;95%, and less nausea and vomiting (&lt;em&gt;P&lt;/em&gt; &lt; .001)</td>
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<td><strong>Control:</strong> Intravenous infusion meperidine 75 mg over 30 min. With insufficient analgesia, another 75 mg administered. Additional 50 mg as needed. Maximum dose 200 mg (range 75-200 mg). Mean total dose 150 mg</td>
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<td><strong>Thurlow et al</strong>&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Randomized controlled trial</td>
<td><strong>Experimental:</strong> PCA remifentanil 20 mcg bolus over 20 s, 3 min lockout interval, no background infusion</td>
<td>Maternal: VAS pain scores 60 min and maximum pain scores during first 2 h after analgesia significantly lower (&lt;em&gt;P&lt;/em&gt; = .0004 and 0.009, respectively) in the remifentanil group. Overall effectiveness of analgesia within 2 h of birth, rated by mothers and midwives, was higher (&lt;em&gt;P&lt;/em&gt; = .002) in remifentanil group. No significant difference between groups in nausea and vomiting. No significant difference in minimum saturation between groups, but authors concluded that the overall saturation may have been lower for women receiving remifentanil.</td>
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<td><strong>Control:</strong> IM meperidine 100 mg, plus promethazine (Phenergan) 25 mg or prochlorperazine (Compazine) 12.5 mg as antiemetic</td>
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<td>Nitrous oxide option available to both groups</td>
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<td>Maternal: No difference between groups in reduction of VAS pain scores 2 h observation. Overall maternal satisfaction higher (&lt;em&gt;P&lt;/em&gt; = .001) with remifentanil. No difference between groups in nausea, anxiety, or maternal desaturation less than 94% or 90%. Sedation increased over time and was similar between groups.</td>
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<td><strong>Fetal:</strong> No change in FHR baseline with both groups. <strong>Labor:</strong> No difference between groups in labor duration. <strong>Newborn:</strong> Neurologic and adaptive capacity scores higher (&lt;em&gt;P&lt;/em&gt; = .003) with remifentanil at 30 min but similar at 2 h after birth. No difference in Apgar scores or cord pH. Naloxone was not used in either group.</td>
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<td>Maternal: No difference between groups in reduction of VAS pain scores during 2 h observation. Overall maternal satisfaction higher (&lt;em&gt;P&lt;/em&gt; = .001) with remifentanil. No difference between groups in nausea, anxiety, or maternal desaturation less than 94% or 90%. Sedation increased over time and was similar between groups.</td>
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<td><strong>Fetal:</strong> No outcomes evaluated.</td>
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<tr>
<td>Douma et al^42</td>
<td>Double-blind, randomized</td>
<td><strong>Experimental:</strong> PCA remifentanil 40 mcg loading dose, 40 mcg/bolus, 2 min lockout interval, maximum dose limit 1200 mcg/h  &lt;br&gt;<strong>Control:</strong> PCA meperidine 49.5 mg loading dose, 5 mg bolus, 10 min lockout interval, total dose limit 200 mg  &lt;br&gt;<strong>Odds Ratio:</strong> PCA fentanyl (Sublimaze) 50 mcg loading dose, 20 mcg bolus, 5 min lockout interval, maximum dose limit 240 mcg/h</td>
<td><em>Labor:</em> Remifentanil associated with more (P = .04) nonvaginal routes of births; 6 of 7 women had also received epidural.  &lt;br&gt;<em>Newborn:</em> No difference in Apgar scores between groups.  &lt;br&gt;<em>Maternal:</em> VAS pain scores decreased in all groups. Greatest decrease in pain scores with remifentanil at 1 h after administration (remifentanil vs meperidine, P &lt; .05; remifentanil vs fentanyl, P &lt; .01; meperidine vs fentanyl, P = NS). At 2 h after initiation of treatment, pain scores with meperidine were no different from baseline, and at 3 h, pain scores were not significantly different from baseline in all groups. Sedation increased in all groups; at 1 h and 2 h sedation was greater with remifentanil compared with meperidine and fentanyl (remifentanil vs meperidine, P &lt; .05; remifentanil vs fentanyl P &lt; .01). At 3 h, sedation scores with remifentanil were greater (P &lt; .05) than with fentanyl only. Itching more common with remifentanil (P &lt; .05). More crossover to epidural in meperidine group (P &lt; .05). No difference in rates of nausea and vomiting. Overall satisfaction after birth greater in remifentanil group when compared with meperidine (P &lt; .05). No difference in satisfaction between remifentanil and fentanyl or meperidine and fentanyl. Remifentanil and fentanyl associated with 1 or more periods of desaturation &lt; 95% compared with meperidine (remifentanil vs meperidine, P &lt; .0001; remifentanil vs fentanyl, P = NS; meperidine vs fentanyl, P &lt; .05).  &lt;br&gt;<em>Fetal:</em> No difference in reactive/nonreactive FHR patterns.  &lt;br&gt;<em>Labor:</em> No difference in duration of labor, oxytocin use. Fentanyl associated with more spontaneous deliveries (P &lt; .05).  &lt;br&gt;<em>Newborn:</em> No difference in Apgar scores, neurologic and adaptive capacity scores at 15 and 120 min, cord blood pH and base excess.</td>
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Abbreviations: FHR, fetal heart rate; IM, intramuscular; NS, not significant; PCA, patient-controlled analgesia; VAS, visual analogue scale.

issues, and it found that 6.3% of newborns exposed to intrapartum remifentanil had breastfeeding difficulties.

**Clinical Considerations**

Depending on dosing regimen, remifentanil may produce modest pain relief for time-limited periods, with associated sedation and periods of maternal oxygen desaturation that may be corrected by oxygen supplementation or a dose reduction. Because remifentanil is a potent respiratory depressant, its intrapartum use requires continuous monitoring of parturients. Recommended guidelines for safe practice include 1-to-1 nursing supervision, continuous pulse oximetry, evaluation of sedation scores every 30 minutes, no other
opioid use during the 4 previous hours, and clear indications for contacting the anesthesia provider (eg, excessive sedation, not responsive to voice, respiratory rate less than 8 breaths per minute, or SpO2 of less than 90% while breathing room air). Women should be informed of potential side effects, including a 10% chance of requiring supplemental oxygen.64 Although no studies have reported low Apgar scores or effects, including a 10% chance of requiring supplemental oxygen.64 Although no studies have reported low Apgar scores or a need for neonatal naloxone, naloxone and resuscitation support should be available for the newborn at the time of birth. Newborns exposed to remifentanil during the intrapartum period may need additional breastfeeding support while establishing breastfeeding.

Current studies are limited by short observation periods, small samples, differing routes of administration, and concomitant nitrous oxide use. More extensive controlled studies are needed to evaluate dosing regimens and safety for laboring women and newborns, including implications for breastfeeding behaviors.

**BUTORPHANOL TARTRATE**

Butorphanol tartrate is a synthetic opioid agonist-antagonist with antagonist activity at mu opioid receptors and agonist activity at kappa opioid receptors.50 Metabolism takes place in the liver, where butorphanol’s primary and inactive metabolite, hydroxybutorphanol, is produced.6 Butorphanol has an analgesic and respiratory ceiling effect such that higher doses do not provide any additional pain relief or respiratory depression but will increase the likelihood of other side effects.

**Efficacy and Side Effects of Butorphanol**

Maternal side effects may include somnolence, sedation, nausea, vomiting, and respiratory depression. A transient pseudosinusoidal fetal heart rate pattern has been associated with butorphanol.55 Neonatal neurologic and adaptive capacity scores have results similar to those of meperidine.

Four double-blind randomized controlled trials34,36,66,67 have compared butorphanol with meperidine for labor pain analgesia and found no significant difference in most outcomes. Three of the trials36,66,67 compared 1 to 2 mg of intramuscular butorphanol to 40 to 80 mg of intramuscular meperidine and found no differences in pain relief, nausea and vomiting, fetal heart rate patterns, Apgar scores, umbilical cord gas values, or neonatal resuscitation requirements.66 With intravenous comparisons, 1 study demonstrated better analgesia with butorphanol (95% CI, −1.02 to −0.18),67 and the other found no difference.36 Less nausea and vomiting (95% CI, 0.00-0.67) was associated with butorphanol in 1 intravenous comparison,48 and no difference was found in another.67 There were no differences between groups in sedation, Apgar scores, or neonatal neurologic and adaptive capacity scores. In a fourth study,34 a combination of 25 mg intravenous meperidine plus 0.5 mg butorphanol was compared with 50 mg intravenous meperidine or 1 mg intravenous butorphanol. All 3 groups had similar reductions in pain intensity following treatment. Sedation increased to a similar degree in all 3 groups, and there was no difference in decreased fetal heart rate variability, nausea, or Apgar scores. A transient sinusoidal fetal heart rate pattern was identified in 1 woman in the meperidine group and 1 in the combination group.

Intravenous butorphanol for labor analgesia also has been compared with intravenous fentanyl. In a double-blind randomized controlled trial,36 investigators demonstrated that women receiving butorphanol (1-2 mg every 1-2 hours) had greater reductions in pain scores (P < .05) during the first hour after dosing compared with women in the fentanyl (50-100 mcg every 1-2 hour) group. As labor pain increased, both groups had only marginal improvements in pain scores, although fewer doses of butorphanol were requested (P < .01). Side effects occurred in both groups, but there was no statistically significant difference in a need for antiemetics (butorphanol 12%, fentanyl 24%), prolonged sedation (butorphanol 8%, fentanyl 4%), or respiratory rate less than 10 breaths per minute (butorphanol 4%, fentanyl 12%). Nor were there differences in rates of decreased fetal heart rate variability (butorphanol 32%, fentanyl 24%), pseudosinusoidal fetal heart rate pattern (butorphanol 20%, fentanyl 10%), or rates of neonatal naloxone use (butorphanol 16%, fentanyl 28%) between groups.

**Effect of Butorphanol on Labor**

Butorphanol has not been associated with a change in uterine contraction patterns for 1 hour after dosing, change in duration of first and second stages of labor, or rate of cesarean birth.50

**Effect of Butorphanol on Breastfeeding**

Butorphanol transports into human milk and has been associated with impaired sucking behaviors during the first 14 hours of life but is not associated with duration of breastfeeding within the first 6 weeks postpartum.68

**Clinical Considerations**

Butorphanol is a high-potency labor analgesic with a ceiling effect for both analgesia and respiratory depression. Two milligrams of intravenous butorphanol produces respiratory depression similar to that of 10 mg of intravenous morphine or 70 mg of intravenous meperidine. However, 4 mg of butorphanol will produce less respiratory depression than 20 mg of morphine or 140 mg of meperidine.69

Although the pseudosinusoidal fetal heart rate pattern associated with butorphanol is thought to be benign, its presence may complicate the interpretation of some fetal heart rate tracings.

Butorphanol is contraindicated for women who are opioid dependent, because the antagonist effects stimulated by this agent may precipitate withdrawal symptoms.

**NALBUPHINE HYDROCHLORIDE**

Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist chemically related to oxymorphone (Opana) and naloxone. Although it binds to mu, kappa, and delta receptors, it is primarily a kappa agonist and partial mu antagonist analgesic. The analgesic potency of nalbuphine is equivalent
to morphine on a milligram-to-milligram basis. Nalbuphine is metabolized to an inactive metabolite. Nalbuphine has a respiratory depression ceiling effect, with a maximum respiratory depression occurring at a dose of 30 mg per 70 kg.70 An analgesic ceiling effect also occurs at these levels.69

Efficacy and Side Effects of Nalbuphine

The most common maternal side effect of nalbuphine when used for labor analgesia is sedation and less frequently nausea, vomiting, drowsiness, and dizziness.71 Respiratory depression can occur and can be reversed with naloxone.70 Undesired fetal effects are temporary decreased fetal heart rate variability71 and decreased number of fetal heart rate accelerations.70 One case report identified a sinusoidal fetal heart rate associated with nalbuphine.72

Studies comparing the effect of nalbuphine with meperidine on labor pain have found conflicting results. Two double-blind, randomized trials found no significant difference in reduction of pain scores with either 10 mg intravenous nalbuphine versus 50 mg intravenous pethidine23 or 20 mg intramuscular nalbuphine versus 100 mg intramuscular pethidine.35 In contrast, another double-blind, randomized trial74 demonstrated that PCA nalbuphine (3-mg increments, maximum 18 mg/hour) when compared with PCA meperidine (15-mg increments, maximum 90 mg/hour) was associated with lower pain scores (P < .01). There were no differences between nalbuphine and meperidine in rates of nausea,35 vomiting,35,71 dizziness,35,71 sedation,35,71 or respiratory rate.71 Apgar scores were no different in 2 trials35,71; more neonates had lower 1-minute Apgar scores in another.73 In 1 trial, nalbuphine was associated with lower neonatal neurologic and adaptive capacity scores (P < .001) at 2 to 4 hours after birth, but there was no difference at 24 hours.35 Another trial found no difference in neonatal neurologic and adaptive capacity scores at 6 to 10 hours.74

Giannina et al70 randomized 28 parturients to receive either 10 mg intravenous nalbuphine or 50 mg intravenous meperidine and examined the effect on intrapartum fetal heart rate patterns 1 hour after administration. Nalbuphine significantly (P = .001) decreased the frequency of accelerations and was associated with more decreased variability (long-term P = .002; short-term P = .03). There were no differences in Apgar scores or umbilical artery pH at birth.

Effect of Nalbuphine on Labor

Studies have found no difference between nalbuphine and meperidine in effects on frequency of uterine contractions,70,74 length of the second stage of labor,74 or mode of birth.70

Effect of Nalbuphine on Breastfeeding

Nalbuphine rapidly transfers to the fetus and is found in small amounts in human milk. This opioid has been associated with impaired sucking behaviors in the first 14 hours of the postpartum period but is not associated with duration of breastfeeding during the first 6 weeks postpartum.14

Clinical Considerations

Although nalbuphine’s respiratory ceiling effects may be of benefit, comparative studies of nalbuphine’s analgesic effect and side effects are inconclusive. Nalbuphine, like butorphanol, is contraindicated for women who are opioid dependent because it may precipitate withdrawal symptoms.

CONCLUSION

Systemic opioids provide little to modest labor pain relief. Pain relief is incomplete, temporary, accompanied by sedation, and more effective in the early part of active labor. Opioids may lack effectiveness after 7 cm of dilation. Despite their limitations, the temporary easing of labor pain following opioid administration may be a helpful and satisfactory pain management strategy for many parturients. For others seeking greater pain relief, the effect of systemically administered opioids may not be satisfactory.

Comparisons of morphine, meperidine, fentanyl, remifentanil, butorphanol, and nalbuphine for labor analgesia demonstrate no significant differences between these opioids for most outcomes. Comparisons of intramuscular administration of meperidine to morphine,22 butorphanol,56 or nalbuphine73 found no significant differences in labor pain relief or maternal and neonatal side effects. Only 1 study35 reported that nalbuphine was associated with lower newborn neuroadaptive scores at 2 to 4 hours of life but no difference at 24 hours.

Comparisons of intravenous opioids for pain relief efficacy are inconclusive. In some studies, butorphanol (167 of 3 studies), nalbuphine (174 of 2 studies), and remifentanil (242,63 of 3 studies) were associated with better labor pain relief than meperidine. Other comparisons of the same drugs found no difference in analgesia effect.27,33,34,36,41,73 Butorphanol50 and remifentanil (142 of 2 studies) were associated with better pain relief than fentanyl. When PCA remifentanil and intramuscular meperidine were compared, remifentanil was associated with better pain relief scores.60

Most comparisons of the adverse effects of intravenous opioids were inconclusive.34,41,50,59,66,73,74 When other opioids were compared with meperidine, several studies found more significant adverse effects associated with meperidine. Compared to meperidine, butorphanol was associated with less dizziness, nausea, and vomiting (136 of 3 studies); fentanyl was associated with less sedation, nausea, vomiting, and naloxone use;33; and morphine appears to cause nausea less often than does meperidine.27 Conversely, desaturation events and sedation were more common with PCA remifentanil and PCA fentanyl than with PCA meperidine42 (1 study). Patient-controlled analgesia remifentanil was associated with less sedation, nausea and vomiting, and desaturation than intravenous meperidine.63

Although it is not clear from comparison studies which opioid is best for labor analgesia, some practical recommendations may be considered based on pharmacokinetic and pharmacodynamic profiles. Opioids with rapid onset and offset of action; rapid metabolism and elimination; minimal undesired maternal, fetal, and neonatal side effects; and lack of active metabolites may be optimal. Although intramuscular opioids have the advantage of simplicity, intravenous
administration may be preferable because it results in rapid onset of pain relief and allows for titration of medication. Intramuscular administration has variable absorption and a delay in onset. Intravenous PCA with fentanyl, morphine, nalbuphine, or remifentanil may provide a more consistent analgesic effect and allow a parturient to control and adjust an opioid to her individual need.

Selecting opioids that have a rapid offset and lack active metabolites may be advantageous to women and newborns. Both meperidine and morphine produce active metabolites, with meperidine's metabolite having the longest half-life and, therefore, more effects on the neonate and breastfeeding behaviors. Other opioids such as fentanyl, remifentanil, butorphanol, and nalbuphine do not have active metabolites. Remifentanil's ultrarapid offset and lack of an active metabolite may be a promising newer alternative; however, more scientific studies are necessary to evaluate maternal and neonatal safety, the effect of dosing on the balancing of pain relief with sedation, and its effect on breastfeeding behaviors.

Scientific investigations of systemic opioids with sufficiently powered studies are still needed so that we may further understand the effect of opioids on pain relief, maternal and neonatal safety, breastfeeding behaviors, and long-term safety. Most studies conducted to date have compared 1 opioid to another or to epidural anesthesia. It may be informative to include in future investigations a comparison group of women and newborns who have not received any analgesics during labor.

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**CONFLICT OF INTEREST**

The author has no conflicts of interest to disclose.

**REFERENCES**


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The Pharmacology of Prostaglandins for Induction of Labor

Susan M. Yount, CNM, PhD, WHNP-BC  Nicole Lassiter, CNM, MSN, WHNP

INTRODUCTION

Synthetic prostaglandins are widely used in obstetrics and gynecology. Although all prostaglandins share the same basic structure, different types and doses are used for various indications such as medical abortion, postpartum hemorrhage, and induction of labor (IOL). Their most common use is for cervical ripening for IOL, in which both endogenous and synthetic prostaglandins play a significant role.1 In the United States, almost one-quarter (22.5%) of all labors are induced, which is more than twice the 9.5% rate of inductions performed in 1990.2–4 This increasing rate appears to be disproportionate to the number of pregnancy complications that are a medical indication for IOL.5

Successful IOL largely depends on the status of the cervix prior to onset of labor.6, 7 Inducing labor when the cervix is firm, long, and closed can result in failed induction and complications including an increased rate of cesarean birth.6, 8 In turn, cesarean birth is associated with an increased risk of complications such as hemorrhage, endometritis, and thromboembolic events.7 The incidence of adverse outcomes following IOL is highest in nulliparous women who have an unfavorable cervix.6, 10 When IOL is attempted for a woman with an unfavorable cervix, other interventions used to aid the induction process, such as oxytocin or rupture of membranes, are associated with reduced effectiveness and high failure rates.6 Therefore, for optimal outcomes, it is critical that obstetric settings have access to affordable, effective prostaglandin medications8 to assist with the process of labor when IOL is indicated.

This article reviews the physiologic role of endogenous prostaglandins and the pharmacokinetics, pharmacodynamics, doses, and routes of administration of the most commonly used exogenous synthetic prostaglandin medications used for IOL. Descriptions and comparisons of safety, efficacy, side and adverse effects, and regulatory profiles of the various medications are presented.

THE CERVIX

Unlike the uterus, which is composed mainly of smooth muscle, the cervix consists primarily of collagen, a fibrous connective tissue that undergoes extensive remodeling and dynamic anatomic and physiologic alterations throughout pregnancy.11 The cervix maintains tremendous weight-bearing potential and tensile strength until gestation is complete. The cervical remodeling process occurs in 4 distinct endocrinologic and structurally unique stages: softening, ripening, dilation, and postpartum repair.12 Softening begins as soon as one month after conception. Size and number of cervical connective tissue cells and cervical glands along with increased edema and vascularity of the cervix lead to cervical softening.1 During this first stage, the cervix gradually begins to change from closed and firm to a more compliant structure; however, it largely maintains its strength and shape during gestation.12

In the ripening phase, the structure and makeup of cervical collagen changes drastically.12 The collagen fibers of the cervix diminish and separate primarily because of the influence of hydrophilic glycosaminoglycans.11 Ripening includes further softening, effacement (shortening of cervical length), and some dilation.12 Ideally, the ripening process occurs several days or weeks before clinical signs and symptoms of labor commence.12, 13 The third phase is dilation of the cervix, which occurs during active labor.1 The fourth and last phase, repair, starts immediately after birth and ends with the completion of uterine involution.1

PHYSIOLOGIC EFFECTS OF ENDOGENOUS PROSTAGLANDINS

Endogenous prostaglandins are 20-carbon eicosanoic fatty acids produced by all bodily tissues.14, 15 The prostaglandin precursor, arachidonic acid, is an essential fatty acid that is
SYNTHETIC PROSTAGLANDINS

Prostaglandins have been used for cervical ripening and IOL since the 1970s. Synthetic prostaglandins mimic the cervical ripening action of endogenous prostaglandins. Although endogenous prostaglandins undergo rapid metabolism in the human body, synthetic prostaglandins have largely been designed to maintain a longer period of bioavailability.

The prostaglandins most commonly used in clinical practice are misoprostol (Cytotec) and dinoprostone (Prepidil, Cervidil). Table 1 lists the pharmacokinetic profiles of the prostaglandins most often used for IOL. A significant amount of data notwithstanding, the optimal prostaglandin medication for IOL is yet to be determined, and questions regarding the safest and most effective dose remain. Randomized trials of prostaglandin agents have assessed dose, route of administration, and comparisons with other prostaglandins as well as other induction agents such as oxytocin and Foley bulb placement. The primary outcome variables of interest have been birth within 24 hours, cesarean rates, and the incidence of uterine hyperstimulation with and without fetal heart rate (FHR) changes.

**MISOPROSTOL: PGE₁**

Misoprostol is a synthetic PGE₁ analogue that has become an important drug in obstetrics and gynecology because of its dual ability to both ripen the cervix and induce uterine contractions. The drug misoprostol is a “synthetic 16-deoxy-16-hydroxy-16-methyl analog of prostaglandin E1 water soluble, viscous liquid.” Misoprostol is approved by the US Food and Drug Administration (FDA) for the prevention and treatment of gastrointestinal ulcers and peptic ulcer disease caused by prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDS). However, misoprostol is widely used off-label for obstetric and gynecologic procedures. Although there are other medications that are FDA approved for IOL, the unique properties of misoprostol set this medication apart from other prostaglandins in that it is low in cost, stable in a wide temperature range, and does not require refrigeration.

In 2002, the FDA revised the warning label for misoprostol to state that it may cause uterine rupture when used for IOL or induced abortion any time after the eighth week of pregnancy per gestational age by last menstrual period. Possible explanations for this restrictive labeling are medicolegal, political, and economic in nature. Uterine rupture associated with misoprostol use is rare; however, when uterine rupture occurs, adverse outcomes are more likely, and liability claims can ensue. Because of its ability to induce abortion, misoprostol can be the subject of highly charged debates. Finally, adding a new indication is a costly process for pharmaceutical companies, and ultimate profits are likely to be low when the medication is already used off-label. Thus, although misoprostol is inexpensive, safe, easy to use, and effective, its FDA-mandated black box warning presents health care providers with a potential medicolegal concern given the availability of other medications currently approved for IOL.

However, the current body of research and evidence supporting the safety and efficacy of the appropriate use and administration of misoprostol for IOL appears sound (see Supporting Information Table S1).
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Generic (Brand)</th>
<th>Dose</th>
<th>Route</th>
<th>Onset of Action (min)</th>
<th>Peak Plasma Level (min)</th>
<th>Plasma half-life (min)</th>
<th>Duration of Action (h)</th>
<th>Mean Time To Sustained UA min</th>
<th>Clinical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E₁</td>
<td>Misoprostol (Cytotec)</td>
<td>25-50 mcg</td>
<td>Oral tablet</td>
<td>12 ± 3</td>
<td>20-30</td>
<td>20-40</td>
<td>2</td>
<td>90</td>
<td>Lower doses associated with less uterine tachysystole but longer time to vaginal birth. EFM and UA monitoring 20-30 min prior to placement and continuously after recommended.</td>
</tr>
<tr>
<td></td>
<td>Misoprostol (Cytotec)</td>
<td>25-50 mcg</td>
<td>Vaginal posterior fornix tablet</td>
<td>20.9 ± 5.3</td>
<td>60-80</td>
<td>60</td>
<td>4.5 to 5</td>
<td>106</td>
<td>EFM and UA monitoring 30 min prior to placement and after for 2-4 h. Repeat every 3-6 h for maximum of 8 doses. Contraindicated with uterine scar.</td>
</tr>
<tr>
<td>Prostaglandin E₂</td>
<td>Dinoprostone (Prepidil)</td>
<td>0.5 mg in 2.5-mL syringe</td>
<td>Endocervical gel</td>
<td>Rapid onset</td>
<td>60-120</td>
<td>Variable</td>
<td>127</td>
<td>Lie recumbent 30 min after insertion. EFM and UA monitoring 2 h before and after insertion. May start oxytocin 6-12 h after insertion. May repeat in 6-12 h for maximum of 3 doses in 24 h. Contraindicated with abnormal FHR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dinoprostone (Cervidil)</td>
<td>10 mg, 0.3 mg/h</td>
<td>Vaginal posterior fornix insert</td>
<td>Rapid onset</td>
<td>Unknown</td>
<td>Unknown</td>
<td>NA</td>
<td>FHR and UA monitoring required after placement and for 15 min after removal. Remains in place for 12 h or to onset of active labor. May start oxytocin 30-60 minutes after removal of insert</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EFM, electronic fetal monitoring; FHR, fetal heart rate; UA, uterine activity.
<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Design</th>
<th>Sample</th>
<th>Dose</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meckstroth et al, 2006</td>
<td>RCT to determine uterine activity and plasma levels of oral, buccal, vaginal, and rectal misoprostol</td>
<td>N = 40 women seeking an induced abortion for a pregnancy &lt; 13 weeks’ gestation</td>
<td>400 mcg</td>
<td>Serum levels of all routes except rectal rose gradually and fell slowly. Peak for all but rectal was between 15 and 120 min, with most between 30 and 90 min. Serum MPA peaked in 15 minutes, then declined more rapidly than the other groups. At 30 min both vaginal routes had greater MPA levels than rectal or buccal. Uterine activity became regular at a mean of 110 min. Buccal associated with lowest variability in drug exposure and peak levels.</td>
</tr>
<tr>
<td>Powers et al, 2008</td>
<td>To establish the in vivo release pharmacokinetic and effects of 3 different doses of sustained-release misoprostol vaginal insert over varied durations.</td>
<td>N = 12 healthy, nonpregnant volunteers</td>
<td>100, 200, and 400 mcg</td>
<td>Maximum plasma concentration (C_{max}) values for the vaginal inserts were considerably lower. Time of C_{max} occurred later than the same dose values after oral dosing. Overall systemic exposure to the 200-mcg vaginal insert was almost 3 times greater over 24 h than the same oral dose. C_{max} for the 200-mcg oral dose was reached &lt;30 min after dosing. MPA was eliminated rapidly, with a half-life &lt;60 min. MPA was below quantification by 4 h after oral dosing. 200-mcg vaginal insert C_{max} was reached after 9 h. MPA fell gradually over the next 15 h but was still measurable at 24 h. Misoprostol vaginal insert provides consistent dosing with a range of doses (100-400 mcg) up to 24 h postinsertion.</td>
</tr>
<tr>
<td>Schaff et al, 2005</td>
<td>Randomized crossover trial to determine differences in the pharmacokinetics of sublingual vs buccal routes of misoprostol</td>
<td>N = 10 healthy, nonpregnant women</td>
<td>800 mcg, buccal or sublingual</td>
<td>Buccal administration was acceptable to all 8 users (4 of 10 found sublingual acceptable). Bioavailability was higher for the sublingual route compared to the buccal route. Sublingual resulted in a higher C_{max} compared with buccal (P &lt; .03). Time to maximum plasma concentration was 30 min, similar to results reported for oral administration. Sublingual may be better tolerated at lower doses.</td>
</tr>
</tbody>
</table>
### Table 2. Pharmacokinetic Studies of Misoprostol

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Design</th>
<th>Sample</th>
<th>Dose</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al, 2009</td>
<td>Prospective, comparative study with randomized subjects to compare the pharmacokinetics of repeat doses of misoprostol after vaginal or sublingual administration</td>
<td>N = 20 pregnant women &lt;12 weeks’ gestation requesting surgical abortion</td>
<td>400 mcg</td>
<td>Peak plasma concentration of MPA in the sublingual group was achieved between 20 and 60 min after each dose. Peak plasma concentration in vaginal group occurred after 20 min except for the fourth dose, which took 60 min. Peak plasma level of MPA after each dose of misoprostol was higher and the bioavailability greater after sublingual administration compared with vaginal administration. Peak plasma levels of MPA decreased with successive doses of vaginal misoprostol; however, the levels were similar for successive doses administered sublingually. Heavy vaginal bleeding may have had an impact on the results.</td>
</tr>
<tr>
<td>Zieman et al, 1997</td>
<td>A prospective, comparative study on the pharmacokinetics of vaginal and oral administration of misoprostol</td>
<td>N = 20; 10 pregnant women between 7 and 13 weeks’ gestation seeking abortion and 10 nonpregnant, healthy women using contraception</td>
<td>400-mcg doses (two 200-mcg tablets)</td>
<td>Plasma MPA levels rose quickly for oral misoprostol, peaked between 12.5 and 60 min, fell rapidly by 120 min, and remained low. Plasma MPA levels after vaginal doses rose gradually, reaching maximum levels between 60 and 120 min ($P &lt; .001$ compared with oral route), and declined slowly. MPA plasma levels for the vaginal group were still 61% of the peak level at 240 min. Incidence of side effects was similar between routes and groups; side effects did not correlate to serum levels. Systemic bioavailability of misoprostol administered vaginally was 3 times higher than the oral route. With the slower rise to peak concentration of MPA in the vaginal route, the medication was sustained for a longer period.</td>
</tr>
</tbody>
</table>

Abbreviations: mcg, microgram; MPA, misoprostol acid; RCT, randomized clinical trial.
Pharmacokinetics of Misoprostol

The pharmacokinetic effects of misoprostol are dependent on the route of administration. Misoprostol has advantages over other natural and synthetic forms of prostaglandins; the tablet can be administered orally, rectally, sublingually, or vaginally, and it can be used for both cervical ripening and IOL. The tablet form of misoprostol is available in 100-mcg nonscored tablets or 200-mcg scored tablets that can be divided into 25- or 50-mcg doses. The pharmacokinetic profile of misoprostol includes rapid absorption, extensive metabolism, and rapid excretion. Table 2 presents summary data from the pharmacokinetic studies of misoprostol.

Oral Route of Administration

Misoprostol has been used for IOL as a vaginal insert or administered orally. In 2010, the Cochrane Collaboration published an update to a meta-analysis that assessed the use of oral misoprostol for IOL in women with a viable fetus. These findings were based on 56 randomized clinical trials (RCTs; N = 11,590) divided into 4 groups. The analysis of 10 trials that compared oral misoprostol with vaginal dinoprostone (n = 3368) found oral misoprostol was associated with fewer cesarean births (risk ratio, 0.87; 95% CI, 0.77-0.98), with no significant differences in uterine hyperstimulation or other birth outcomes. Eight trials compared oral misoprostol with intravenous oxytocin (n = 1026). The analysis found an increase of meconium in the amniotic fluid in women with ruptured membranes who used oral misoprostol (risk ratio, 1.72; 95% CI, 1.08-2.74) but again no difference in other birth outcomes. The third group included 7 trials that compared oral misoprostol with a placebo (n = 669). This analysis found that women given oral misoprostol had a lower rate of cesarean birth (risk ratio, 0.61; 95% CI, 0.41-0.93), required less oxytocin (risk ratio, 0.35; 95% CI, 0.28-0.44), and had a higher chance of giving birth vaginally within 24 hours (risk ratio, 0.16; 95% CI, 0.05-.49). The meta-analysis of 26 RCTs (n = 5096) that compared oral versus vaginal misoprostol found no difference in the primary outcomes between the 2 routes of administration. The oral route was associated with a reduction in low Apgar scores at 5 minutes (risk ratio, 0.65; 95% CI, 0.44-0.97) and less uterine hyperstimulation. The authors did comment that heterogeneity between the studies included in the meta-analysis made the finding on hyperstimulation difficult to interpret. The authors concluded that oral misoprostol is as effective as other induction methods for achieving vaginal birth and is associated with lower rates of cesarean birth when compared with vaginal administration of dinoprostone. They recommended that the safest route of administration is oral, using a dose of 20 to 25 mcg. Furthermore, they concluded that research evaluating vaginal use of misoprostol should cease and be redirected to the oral route, as the oral route is associated with safer outcomes. Concerns about uterine hyperstimulation leading to FHR changes with the oral route should be put to rest, as low-dose oral misoprostol resulted in lower uterine hyperstimulation rates when compared with vaginally administered misoprostol. The lower dose recommended for the oral route leads to a longer induction period; however, the outcomes are improved.

Following oral intake, misoprostol is rapidly and extensively metabolized in the liver via the first-pass effect into misoprostol acid (MPA), its primary active metabolite, which is responsible for activity at the cellular level and can be measured in plasma. Time to maximum plasma concentration of MPA after oral administration is 12 ± 3 minutes, with a terminal half-life of 20 to 40 minutes. After oral dosing (≤50 mcg), plasma MPA levels peak in 20 to 30 minutes, then quickly decline by 2 hours, at which point they stay at low levels. Maximum concentrations of MPA in plasma are decreased when food or antacid is ingested with the medication. Most of the drug is metabolized in the liver; less than 1% is excreted in urine.

The biologic activity of oral misoprostol is equivalent to vaginal administration when the oral dose is twice the vaginal dose. Consequently, if 25 mcg is considered the optimal vaginal dose, 50 mcg would be optimal for the oral dose. Research on IOL at term has involved doses ranging from 25 to 200 mcg, with most of the RCTs using a 25-mcg dose. The current recommendation from the Cochrane Collaboration is 25 mcg every 2 hours depending on uterine response. The short half-life provides the opportunity to withhold, maintain, or increase the dose as clinically indicated.

In addition to being effective and associated with less uterine hyperstimulation than other routes of administration, orally administered misoprostol is widely used, acceptable to women, and easily measured for proper administration. Outpatient administration is theoretically a possibility; however, more data and quality reviews are needed to determine feasibility and safety before this can be considered. At this time, use of misoprostol (oral or vaginal) in an ambulatory setting is not recommended because of the need for surveillance of uterine activity to ensure that there are no adverse effects for the woman or fetus.

Sublingual and Buccal Routes of Administration

In 2010, the Cochrane Collaboration published a meta-analysis that assessed the effectiveness of buccal and sublingual administration of misoprostol for cervical ripening and IOL. These findings were based on 3 small RCTs with 502 participants. The meta-analysis found that the buccal route was associated with fewer cesarean births compared with the vaginal route (relative risk, 0.70; 95% CI, 0.42-1.15), with no differences in any other relevant clinical outcomes. When buccal and sublingual dose regimens were compared, the sublingual dose was also associated with fewer cesarean births, less oxytocin use, and fewer failures to achieve vaginal birth within 24 hours, but these results were not statistically significant. For the sublingual route, high bioavailability and rapid onset are likely a result of avoidance of the first-pass effect, ample vasculature under the tongue, and neutral pH.

Tang et al randomized 20 women seeking termination of pregnancy in the first trimester to administration of misoprostol vaginally or sublingually. They compared the pharmacokinetics of both routes of administration after repeat doses (5 doses given every 3 hours). The peak plasma levels of misoprostol administered sublingually remained consistent,
with sequential doses leading to greater bioavailability of the drug over time; MPA then dropped to a negligible level after 4 hours.\textsuperscript{34}

A randomized crossover trial to determine if significant differences existed between the pharmacokinetics of buccal versus sublingual misoprostol was conducted by Schaff et al.\textsuperscript{31} Their small study included 10 healthy, nonpregnant female participants.\textsuperscript{31} The women took 800-mcg tablets of misoprostol via either the buccal or sublingual route once, with a 4-day washout period between alternating routes. Sublingual dosing was associated with the highest plasma concentration, the most bioavailability, and more adverse effects\textsuperscript{31} relative to all other routes of administration.\textsuperscript{31,34} This may be because there is more blood circulation in the sublingual area compared with the buccal site, which results in extensive absorption of the drug.\textsuperscript{31} In addition, portions of the buccal dose may have been swallowed, activating a more extensive metabolism of the drug. Maximum plasma concentrations for the buccal route were achieved at 30 minutes. Bioavailability\textsuperscript{31} was similar to the findings for oral and vaginal routes previously reported in the literature.\textsuperscript{31,35}

In summary, MPA plasma levels peak faster after oral administration than after vaginal administration. Metabolism of MPA is also faster after oral administration. Following 200-mcg doses, sustained plasma levels of MPA have been detected at an approximately 3-fold increase 24 hours after vaginal administration compared with oral administration.\textsuperscript{35} The buccal route has the least variability with the same uterine response as vaginal administration. The use of sublingual or buccal misoprostol cannot be recommended at this time.\textsuperscript{30,31,33} The question remains whether increased, improved, or enhanced bioavailability results in a better clinical effect. Much of the pharmacokinetic research on misoprostol has been conducted with healthy, nonpregnant women or women less than 13 weeks’ gestation seeking pregnancy termination. Future research is needed on the sublingual or buccal alternative oral routes for IOL.

**Vaginal Route of Administration**

Dodd et al conducted a systematic review of the effectiveness and safety of misoprostol for IOL in women in the second or third trimester who had fetal anomalies or intrauterine fetal demise. The review included 38 RCTs with 3679 women.\textsuperscript{36} The review found that vaginal misoprostol is as effective for inducing labor and achieving birth within 24 hours with fewer maternal side effects compared with other vaginal prostaglandin preparations (eg, Gemeprost, PGE\textsubscript{2}, and PGF\textsubscript{2\alpha}).\textsuperscript{36} Cumulative doses ranged from 400 to 3200 mcg within a 24-hour period, which are higher doses than those used for women undergoing IOL at term.\textsuperscript{36} The dosing intervals ranged from every 3 to every 12 hours.\textsuperscript{36} At these high doses, women given vaginal misoprostol had diarrhea, nausea, and vomiting less frequently than women given other prostaglandin preparations.\textsuperscript{36}

Another 2010 Cochrane review, by Hofmeyr et al, was conducted to determine the effects of vaginal administration of misoprostol for cervical ripening or IOL at term. The meta-analysis included 121 RCTs, of which 13 were double blinded. Vaginal administration of misoprostol at 25 mcg given every 4 hours compared with vaginal administration of dinoprostone gel or intravenous administration of oxytocin was associated with fewer failures in achieving vaginal birth in 24 hours and less epidural use but more uterine hyperstimulation with and without FHR changes.\textsuperscript{7} When compared with women who solely used other vaginal induction agents, women who used vaginal misoprostol required less oxytocin augmentation, whereas meconium-stained fluid was more common.\textsuperscript{7} Vaginal administration of misoprostol may have a clinical benefit over other vaginal prostaglandin preparations for IOL; however, oral misoprostol may prove to be safer given that it is associated with fewer side effects such as uterine hyperstimulation.\textsuperscript{7,36}

Because misoprostol tablets are not designed for vaginal administration, slow or erratic absorption may occur.\textsuperscript{26} Broken fragments of a 100- or 200-mcg tablet may not accurately equal 25 mcg,\textsuperscript{7} which could increase the risk of inaccurate dosing. After vaginal administration, absorption of misoprostol has been found to be inconsistent,\textsuperscript{25} but as noted previously, peak plasma levels are generally slightly lower than are peak plasma levels that result after oral dosing.\textsuperscript{25,27} In addition, misoprostol tablets mixed with water do not appear to change the bioavailability of the drug, and vaginal pH has no effect on the efficacy of this route.\textsuperscript{33} The longer times to peak plasma concentrations, slightly reduced plasma concentrations, and longer drug exposure for the woman,\textsuperscript{3,33} along with less cost and greater drug stability,\textsuperscript{33} make vaginal administration an attractive option compared with other routes. However, these benefits should be viewed in light of the more frequent incidence of uterine hyperstimulation when compared with oral misoprostol.

Crushing the tablet and reconstituting into a gel is not recommended. Stability of the compound and uniformity of the dose are not guaranteed when the formula has been altered.\textsuperscript{33} In addition, chemical properties may be altered if the tablet is exposed to lubrication gel, which could inactivate the misoprostol.\textsuperscript{33} Use of a pill inserter would bypass the effect of lubricant on the tablet,\textsuperscript{33} yet this could limit availability. Care should be taken when deciding on formulation and insertion practices so women receive optimal results from vaginal administration of this drug.

**Protocols for Vaginal Administration of Misoprostol**

Misoprostol tablets are inserted vaginally for cervical ripening or IOL with established protocols. A typical dosing regimen is 25 to 50 mcg intravaginally.\textsuperscript{37} The 25-mcg dose was associated with less uterine hyperstimulation with and without FHR changes in the Cochrane meta-analysis when compared with a 50-mcg dose (16 trials; relative risk, 0.51; 95% CI, 0.37-0.69).\textsuperscript{7} The American College of Obstetricians and Gynecologists (ACOG) recommends insertion of a 25-mcg dose into the posterior vaginal fornix repeated every 3 to 6 hours as needed.\textsuperscript{3,7,28} A study conducted in 1995 reported that 25 mcg given every 3 hours (maximum of 8 times) was found to be more efficacious than 25 mcg administered every 6 hours.\textsuperscript{19} Doses of 50 mcg every 6 hours may be appropriate in some circumstances;\textsuperscript{1} however, ACOG warns that higher doses (50 mcg every 6 hours) are associated with more uterine hyperstimulation and FHR decelerations.\textsuperscript{3}
**Side Effects of Misoprostol**

Repeat dosing of misoprostol is not based on systemic plasma levels of MPA but on cervical and uterine response; however, the plasma levels help providers adhere to the toxicology and pharmacologic safety data formulated for oral misoprostol. Misoprostol is associated with few systemic side effects. The most common side effects are diarrhea and shivering which are short-lived. Less common side effects include headache, menstrual cramps, nausea, flatulence, chills, fever, and vomiting. Side effects associated with the oral route are mainly gastrointestinal: gastric upset, vomiting, indigestion, constipation, and diarrhea; these side effects are reduced with the vaginal route.

Authors of a Cochrane systematic review reported that side effects did not correlate with plasma levels of the drug; however, other research has reported that route and higher doses are associated with more side effects. Misoprostol has no known drug interactions.

**Adverse Effects of Misoprostol: Uterine Hyperstimulation**

Misoprostol is a highly effective uterotonic. Although this serves a useful clinical purpose, excessive dosing can cause precipitous labor, uterine hyperstimulation, or hypertension, leading to adverse maternal and perinatal outcomes. Uterine hyperstimulation with or without FHR changes is more frequent with vaginal misoprostol compared with oral dosing. A clear, positive relationship exists between the dose of oral misoprostol and the incidence of uterine hyperstimulation with FHR changes. Uterine hyperstimulation with FHR changes has not been associated with adverse neonatal outcomes, but there is an increased risk for cesarean birth with vaginal versus oral dosing.

**Contraindications to Use of Misoprostol**

Prostaglandin use for IOL or cervical ripening is contraindicated in women attempting a vaginal birth after cesarean (VBAC). The rate of uterine rupture with the use of misoprostol on a scarred uterus is unknown; however, a retrospective observational study from one institution in Turkey reported a 9.7% rate of uterine rupture in women with a previous cesarean who were administered 50 mcg of misoprostol vaginally for IOL compared with women without a history of uterine surgery who received 50 mcg of misoprostol vaginally for IOL (4 of 41 vs 0 of 50 women, respectively; $P < .001$). Aslan et al reported one dose of vaginal misoprostol was effective for cervical ripening in 74% of women with a previous uterine scar. The remaining women in the study were given 100 mcg of misoprostol orally every 4 hours for up to a total of 6 doses if they had not yet met the cervical ripening criteria or progressed to active labor. Women with uterine scarring were more likely to have oxytocin augmentation after the ripening process than women without uterine scarring (41% vs 20%; $P = .037$). In 1999, Plaut et al reported a 5.6% rate (5 of 89 case reports) of uterine scar rupture with the use of vaginal misoprostol for IOL in women who had a prior cesarean, compared with a rupture rate of 0.2% among women with a prior cesarean who had undergone a trial of labor without misoprostol use. Although it is uncertain if misoprostol alone increases the frequency of uterine rupture, the recommendation is not to administer this drug to women who have a uterine scar from prior surgery. There was no reported incidence of uterine rupture among the women who had a previous cesarean in the Cochrane systematic review that evaluated vaginal versus oral misoprostol (25 mcg, $n = 27$; and 200 mcg, $n = 131$). If labor and/or birth are not indicated, the use of misoprostol for pregnant women is contraindicated.

**Dinoprostone: PGE₂**

Dinoprostone, which is synthetic PGE₂, is FDA approved for cervical ripening or IOL. There are 2 FDA-approved forms of dinoprostone for cervical ripening: a vaginal insert (Cervidil) and cervical gel (Prepidil). Dinoprostone is expensive and requires cold storage to keep the compound chemically stable, which hinders ease of use.

**Pharmacokinetics of Dinoprostone**

Dinoprostone is more difficult to measure than other prostaglandins because of its rapid metabolism and unstable levels in plasma. Detectable levels can be found in plasma after vaginal administration of dinoprostone tablets, thus exhibiting systemic absorption via vaginal mucosa. The cervical gel releases prostaglandins at a faster rate than the vaginal insert; however, vaginal administration is associated with a gradual increase in plasma levels and a longer duration of action. MacKenzie et al, in a 1987 seminal study, detected plasma levels of all formulations of PGE₂ (wax pessary, gel, tablet [0.5 and 3 mg], and polymer [10 mg with a half-life of 4 hours and 10 mg with a half-life of 7 hours]), proving that MPA reaches systemic circulation. The comparative study included 35 women seeking abortion between 15 and 18 weeks’ gestation. The wax pessary, with peak levels 1 to 2 hours after treatment, displayed, at 30 minutes, the quickest release of MPA crossing the vaginal mucosa into systemic circulation. Dinoprostone is subsequently excreted in the urine.

**Cervical Gel**

Prepidil was the first prostaglandin gel commercially available for cervical ripening receiving FDA approval in 1993. Dinoprostone cervical gel is packaged with 2 catheters and a syringe that contains 0.5 mg of dinoprostone. The gel must be refrigerated and thawed prior to insertion into the external cervical os. The initial dose of cervical gel is 0.5 mg in 2.5 mL of gel, which is inserted endocervically just below the level of the internal os. According to the manufacturer, the total maximum dose of dinoprostone within a 24-hour period is 1.5 mg (3 doses, which is 7.5 mL of Prepidil gel).

Per the manufacturer’s recommendations, women must remain supine for a minimum of 30 minutes after insertion. The gel application can be repeated 6 to 12 hours after initial application by inserting an additional 0.5 mg. Oxytocin augmentation should not be initiated until 6 to 12 hours after the final dose.
**Vaginal Insert**

Cervidil is a sustained-release formulation of dinoprostone that must be frozen but does not require thawing prior to vaginal insertion. The insert is a thin, flat, rectangular-shaped chip with rounded corners containing 10 mg of dinoprostone, all encased within a sleeve of knitted polyester that has a tail for removal. Placement varies depending on provider choice. Providers may wrap the string around the insert moistened with water so it is one small unit or leave the string hanging intravaginally. The insert is placed sideways in the posterior fornix allowing for maximum moisture absorption, expansion of the insert, and release of the medication at a controlled rate. The insert releases dinoprostone at a rate of 0.3 mg per hour for 24 hours. The insert should be removed after 12 hours or if the woman is in active labor.

Kalkat et al conducted an RCT comparing 2 dinoprostone preparations (gel and a slow-release pessary) and reported that both were effective for IOL, with insignificant differences in induction to birth times, mode of birth, neonatal outcomes, and birth within 24 hours. The RCT included 120 women, of whom 60 were allocated to intravaginal administration of gel (Prostin) and 60 to a slow-release pessary (Propress). The women in the pessary group had significantly fewer vaginal examinations than did the women in the gel group (5.0 [2.2] vs 6.2 [2.7], P = .012). The authors reported that fewer vaginal examinations resulted in less invasiveness along with increased patient comfort and therefore greater patient satisfaction. Fewer vaginal examinations also led to reduced midwifery hours per patient, potentially reducing cost. Approximately 2% of women reported temperature elevation with both the pessary and gel routes, but vomiting occurred only with the pessary. Diarrhea only occurred in the women who received the gel formulation.

**Adverse Effects of Dinoprostone**

Uterine hyperstimulation is the most significant adverse effect of dinoprostone administration. Uterine hyperstimulation with FHR changes occurs at a 1% rate with gel and at a 5% rate with the vaginal insert starting one hour after administration and lasting up to 9.5 hours. Uterine hyperstimulation and FHR abnormalities caused by vaginal administration of dinoprostone resolved within 15 minutes of removal and did not result in an increase in operative birth secondary to fetal distress. The ability to remove the drug quickly and easily is an advantage of this method.

A systematic review of studies that included pregnant women with a live fetus in their third trimester of pregnancy requiring IOL was recently performed. Uterine hyperstimulation with FHR changes was increased with vaginal dinoprostone use compared with placebo in 14 trials with 1259 women (relative risk, 4.14; 95% CI, 1.93-8.90). An additional 13 trials (N = 3636) found an increase in uterine hyperstimulation without FHR changes for vaginal dinoprostone compared with placebo (relative risk, 2.48; 95% CI, 1.17-5.26). These trials had insufficient data about neonatal morbidity or death, limiting the ability to draw conclusions regarding the clinical adverse effects associated with uterine hyperstimulation. Dinoprostone gel was not associated with an increased risk of hyperstimulation with FHR changes. However, more hyperstimulation without FHR changes was found among 2531 women in 11 trials (relative risk, 1.59; 95% CI, 1.09-2.33). When the vaginal insert was compared with cervical gel, no differences were found for uterine hyperstimulation in 29 trials including 3881 women.

A secondary analysis of a multisite, double-masked, randomized trial of 1308 women requiring cervical ripening before IOL focused on the timing, incidence, and clinical outcomes after administration of either dinoprostone or misoprostol vaginal inserts. Women in the dinoprostone intravaginal group were more likely to have hyperstimulation, hypertonus, and/or tachysystole than the women given 50- or 100-mcg vaginal inserts of misoprostol while the drug was in situ (P <.001). There was no difference in FHR abnormalities between the 2 prostaglandin preparations and no overall difference in cesarean rates for FHR abnormalities. Few (6 of 130) of the abnormal uterine events that led to a cesarean birth were emergent in nature, and none of the newborns were admitted to the neonatal intensive care unit or had an Apgar score of 6 or lower at 5 minutes.

**Contraindications to Dinoprostone**

Like misoprostol, dinoprostone is contraindicated for women attempting a VBAC. Women attempting a VBAC using dinoprostone for IOL experienced uterine rupture 2.5% to 3.9% of the time compared with 0.45% to 0.7% for these women going into spontaneous labor. Martinez de Tejada et al reported the outcomes of 403 women with preeclampsia who received dinoprostone or misoprostol for cervical ripening. Women with a prior cesarean were excluded from the study, and 57% were nulliparous. Placental abruption occurred more frequently in the women in the dinoprostone group compared with the women in the misoprostol group (5.4% vs 1.3%, P = .03). Misoprostol use with hypertensive women was not associated with a higher risk of placental abruption than other prostaglandins. The current recommendation is to use dinoprostone with caution in women with hypertension as well for women with glaucoma, asthma, and severe hepatic or renal dysfunction.

Dinoprostone is a bronchodilator. Misoprostol and dinoprostone are not contraindicated in women with asthma. Presently there has been no reported incidence of significant blood pressure changes or bronchoconstriction after use of low-dose gel.

**Dinoprostone Summary**

Dinoprostone in the form of a vaginal insert or cervical gel has been in use for IOL for more than 15 years. Although the gel may initially be more efficient because of quicker onset of action, the vaginal insert has a longer duration of action. However, both are considered equally effective in overall time to birth, mode of birth, and neonatal outcome. Both forms of dinoprostone are expensive compared with other induction agents and require refrigeration, which adds to cost and the need for special resources (compared with misoprostol, which may be stored at room temperature). A significant benefit of the gel is its usability in both inpatient and outpatient settings.
yet the vaginal insert may be associated with fewer vaginal examinations and can be removed swiftly if needed. Adverse effects of both the insert and the gel are minimal. Finally, both forms of dinoprostone have similar contraindications. When choosing dinoprostone for IOL, choice of one agent over another will depend on availability, resources, and management plan for the particular clinical setting.

THE MOST EFFECTIVE ROUTE FOR INDUCTION OF LABOR

Controversy exists regarding the use of misoprostol for IOL. The vaginal and oral routes of administration appear as effective or better than other induction methods and are similar in effectiveness and outcomes compared with each other. Comparing data for these routes is difficult because of multiple variations in doses in the many RCTs that have been performed.

Buccal misoprostol presents an alternative route resulting in similar uterine response when compared with the dry and wet tablet vaginal routes. Compared with the vaginal route of administration, the buccal route resulted in fewer cesarean births. Misoprostol given orally compared with vaginally has fewer occurrences of uterine hyperstimulation with FHR changes and fewer abnormal FHR patterns, which suggests the oral route of administration may be safer for the fetus. However, it is important to remember that none of the episodes of uterine hyperstimulation with FHR changes that were observed in the trials were associated with an adverse newborn outcome.

A 2003 Cochrane review compared the efficacy and safety of dinoprostone vaginal inserts and misoprostol tablets administered vaginally for third-trimester cervical ripening and IOL and found no statistically significant difference in the rate of cesarean birth, mode of birth, or fetal and neonatal adverse outcomes between the 2 different prostaglandins. However, compared with vaginal or intracervical dinoprostone, women given misoprostol vaginally required less oxytocin augmentation, whereas meconium-stained fluid occurred more often.

Tan et al conducted an RCT that compared a 3-mcg dinoprostone pessary with 25-mcg misoprostol pessaries (single or double dose) for cervical ripening. Most of the 171 women in their study achieved a favorable cervix or active labor by day 2; however, the single dose was less efficacious, and parity was the only significant factor that influenced the outcome. More multiparous women had a favorable cervix or active labor compared with primiparous women (odds ratio [OR], 0.21; 95% CI, 0.06-0.77). Finally, a meta-analysis of RCTs (N = 1572) found vaginally administered misoprostol was more effective than the dinoprostone vaginal insert for IOL and cervical ripening, and the medications had similar safety profiles.

In summary, misoprostol and dinoprostone have similar safety profiles and outcomes. Misoprostol has active metabolites that result in a longer duration of action when compared with vaginal administration of dinoprostone; however, absorption of misoprostol is variable. Lower cesarean rates are seen when oral misoprostol is used for IOL compared with other induction methods and routes. Oral misoprostol is associated with higher 5-minute Apgar scores primarily compared with vaginal misoprostol.

An oral dose of misoprostol peaks quickly in plasma and is metabolized quickly which is probably why oral dosing is associated with fewer side effects than is vaginal dosing. In general, oral administration appears advantageous. Even the 2010 Cochrane review reported that the oral route of administration is preferable to the vaginal route.

IMPLICATIONS FOR PRACTICE

Pharmacologic research on prostaglandins has been performed for decades. The current recommendation is to focus on establishing an ideal route of administration, safety, and dose from which to formulate evidence-based practice guidelines. Buccal and sublingual forms of prostaglandins could be of value for IOL or cervical ripening. They both have a more rapid onset and higher bioavailability and are more acceptable to women than vaginal administration. Neither buccal nor sublingual misoprostol should be used for IOL until larger clinical trials determine safety and optimal dosing. Research is still being conducted on these alternative oral routes and should be supported to enhance options for preparing or inducing labor.

Reviews of RCTs have consistently shown that misoprostol has advantages over dinoprostone for IOL and cervical ripening. Misoprostol is more efficacious than dinoprostone, has better safety profiles, and is more cost-effective. This statement is important for evidence-based practice, as dinoprostone has been the standard of practice for cervical ripening and prostaglandin-based IOL methods. The FDA has not approved misoprostol for IOL, but it is commonly used off-label. Misoprostol is recommended by ACOG as a safe alternative for cervical ripening. Misoprostol administered as 25 mcg every 3 to 6 hours or 50 mcg every 6 hours is safe and effective for cervical ripening in women with term pregnancies. Current recommendations are based on research that has found oral misoprostol to be as effective as vaginal misoprostol and safer than vaginal dinoprostone. Evidence-based practice points are listed in Box 1.

CONCLUSION

For more than 40 years, synthetic prostaglandins have played a key role in obstetric and gynecologic settings. The available evidence base from which to choose the safest and most effective agent for the IOL continues to grow. Although use of misoprostol for IOL is off-label, it is widely used both nationally and internationally, which has led to numerous studies and improved administration techniques for this popular medication. Many concerns regarding the adverse effects of misoprostol involve dose and dosing intervals no longer in use. Even so, additional research is needed to support or refute current findings and further determine the safest and most effective dose regimens. Midwives and members of the obstetric team can use best evidence about prostaglandins to guide management and avoid unsafe practice.
Box 1. Summary Recommendations for Clinical Use of Prostaglandins

**Oral Misoprostol (Cytotec)**
- Low cost
- Noninvasive
- Stable at room temperature
- Short time to effectiveness—peaks rapidly then declines by 2 hours
- Bioavailability equivalent to vaginal misoprostol (when oral dose is double the vaginal dose)
- Bioavailability reduced by high-fat meal
- More accurate dosing than vaginal administration
- Less uterine hyperstimulation with FHR changes compared with vaginal misoprostol
- 25 to 50 mcg safe for IOL and cervical ripening in term pregnancies
- Similar in effectiveness and outcomes to vaginal route and better than other induction methods
- Better 5-minute Apgar scores than other methods/routes
- Lower cesarean rates than other methods/routes
- Cochrane Collaboration states oral route is preferable to vaginal route
- Future research needed to determine proper dose for safety

**Vaginal Misoprostol (Cytotec)**
- Low cost
- Stable at room temperature
- More sustained plasma levels than oral route (bypasses first-pass effect) with longer exposure
- Longer onset of action than oral route
- More effective for cervical ripening and IOL than oxytocin or dinoprostone
- Fewer failures of birth within 24 hours of administration, less epidural use, and less oxytocin use than dinoprostone or oxytocin
- More uterine hyperstimulation and meconium-stained fluid compared with other vaginal induction methods
- Slow or erratic absorption can occur
- May result in inaccurate dosing
- American College of Obstetricians and Gynecologists recommends 25 mcg every 3 to 6 hours, ideally every 4 hours

**Dinoprostone Cervical Gel (Prepidil)**
- Must be kept refrigerated and thawed to room temperature prior to use
- Insignificant difference in induction to birth times, mode of birth, neonatal outcomes, and birth within 24 hours when gel and insert are compared
- Uterine hyperstimulation with FHR changes occurs in 1% of women starting one hour after administration
- Lower efficacy than vaginal misoprostol for birth within 12 and 24 hours and increased need for oxytocin augmentation

**Dinoprostone Vaginal Insert (Cervidil)**
- Cold-stored (frozen) but no need to thaw
- Potentially decreases number of vaginal examinations
- No difference in indication for cesarean birth, mode of birth, and fetal or neonatal adverse outcomes compared with vaginal misoprostol
- Uterine hyperstimulation with FHR changes occurs in 5% of women starting one hour after administration
- Able to remove drug quickly, and FHR changes resolve within 15 minutes after removal

Abbreviations: FHR, fetal heart rate; IOL, induction of labor.

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**CONFLICT OF INTEREST**
The authors have no conflicts of interest to disclose.

**REFERENCES**

Continuing education units (CEUs) for this article are available. To obtain CEUs online, please visit www.jmwhce.org. A CEU form that can be mailed or faxed is available in the print edition of the theme issue.
Preterm birth is the leading cause of perinatal morbidity and mortality and leads to significant health care costs annually. Despite numerous advances in the care of obstetrical patients, the incidence of preterm birth in the United States is at an all-time high and may be on the rise given current trends of advancing maternal age, maternal medical conditions, assisted reproductive technology, and multiple gestations. Neonatal morbidity is strongly associated with gestational age at birth with adverse neonatal outcomes occurring in 77% of those born at 24 to 27 weeks’ gestation compared with only 2% born at or beyond 34 weeks. Therefore, prevention of preterm birth and its associated neonatal morbidity and mortality are major worldwide concerns and a significant focus for obstetrical research.

Certain maternal factors have been identified that increase the risk of preterm birth. African-American women have consistently higher rates of preterm birth ranging from 16% to 18% compared with 5% to 9% of Caucasian women. Also, women with a prior history of preterm birth have a 2.5-fold increased risk of preterm delivery in a subsequent pregnancy, although this risk may be reduced with progesterone supplementation. Additional risk factors include low socioeconomic status, poor nutritional status, maternal medical conditions, extremes of maternal age, smoking, and history of cervical conization.

Preterm labor is thought to be a multifactorial process with an underlying infection as the initiating factor in at least 25% to 40% of preterm births. Microorganisms within the upper genital tract cause activation of the immune response with production of inflammatory cytokines and prostaglandins that result in uterine contractions and weakening of the amniotic membranes. Despite this association between infection and preterm delivery, antibiotics have not been shown to decrease the risk for preterm birth. Tocolytics have also not been shown to decrease the risk for
preterm birth, but they have been shown to temporarily inhibit uterine contractions. In a systematic review including 18 randomized, controlled trials comparing a tocolytic versus placebo or no treatment for preterm labor, tocolysis decreased the risk of delivery within 48 hours and 7 days, but did not prevent preterm birth before 37 weeks.8

Given the short-term delay in delivery with tocolysis, the primary goal of tocolytic therapy is to allow administration of glucocorticoids to reduce the risk of the prematurity-related complications of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. In addition, a second goal of tocolytics is to allow for maternal transport to a facility capable of providing more advanced neonatal care. Tocolysis may be discontinued when these goals are met or when the maternal or fetal risk of pregnancy continuation or drug exposure outweighs the morbidity associated with preterm birth, generally around 34 weeks’ gestation.9 Contraindications to tocolysis include evidence of intra-amniotic infection, intrauterine fetal demise, lethal fetal anomalies, severe fetal growth restriction, preeclampsia, or nonreassuring fetal status. In this article, we review the various tocolytics used for preterm labor and examine their mechanisms of action, efficacy, dosing, and side effects.

MAGNESIUM SULFATE

Magnesium sulfate is the most commonly used tocolytic agent in the United States.10 It was first evaluated for tocolysis in the 1970s.11 Although the mechanism of action is not completely understood, it is thought to be related to its antagonistic action with calcium. A predominant portion (99%) of magnesium is intracellular, localized to bones, myocytes, nuclei, microsomes, and mitochondria. Of the 1% that is extracellular, 62% circulates ionized in the maternal serum.12,13 Magnesium functions at the extracellular and intracellular levels, decreasing the availability of calcium by blocking membrane and intracellular calcium channels, which decreases myometrial contractility.14,15

Magnesium sulfate has failed to show benefit or superior efficacy to other tocolytics in multiple systematic reviews, yet it is still commonly used today. In a systematic review of 4 randomized trials evaluating the efficacy of magnesium sulfate compared with placebo or no therapy for preterm labor, there was no reduction in the frequency of delivery within 48 hours, 7 days, or before 37 weeks gestation. There was also not a reduction in the outcome of newborn birth weight of less than 2500 grams. In addition, no single study was able to show an improvement in the more common newborn morbidities of respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis.16 Comparison of magnesium sulfate with other tocolytics does not show magnesium to be more efficacious than other tocolytics. In this same systematic review, magnesium sulfate was compared with beta-mimetics, calcium channel blockers, and cyclooxygenase (COX) inhibitors in 15 studies. Magnesium sulfate did not show improved length of gestation or neonatal benefit compared with the other tocolytics.

Standard administration doses for magnesium include a 4- to 6-g loading dose over 20 to 30 minutes followed by a continuous infusion of 2 g/h. Titration may be necessary depending on contraction frequency and tolerance of drug. It is contraindicated in women with myasthenia gravis and should be used in caution in the setting of renal insufficiency because it is excreted by the kidneys. Impaired renal function may quickly lead to toxicity at normal doses. In patients with renal insufficiency (serum creatinine >1.0 mg/dL), a loading dose is acceptable but the maintenance dose should be held or kept at 1 g/h.17

Maternal side effects, which range from mild to severe, are seen in up to 60% of exposed women and include flushing, nausea, blurry vision, headache, lethargy,
Magnesium toxicity is related to serum concentration level. Loss of patellar reflexes may be the first clinical sign of toxicity followed by decreased urine output (<100 mL/4 h). Reflexes and urine output should be monitored closely during administration. Although rare, respiratory depression and arrest can occur at levels above 10 to 12 mg/dL, so the medication should be stopped and serum level checked if there is clinical concern for toxicity.

Controversy around the effect of magnesium sulfate on the fetus and neonate has been cited in the literature. Magnesium has been shown to decrease fetal heart rate baseline and variability, but these do not have clinical significance. Other studies have shown adverse neonatal effects from magnesium exposure. In a randomized, controlled trial by Lyell and colleagues comparing magnesium sulfate with nifedipine for tocolysis, infants exposed to magnesium had an increased rate of neonatal intensive care unit (NICU) admission and longer NICU stays. Other authors have suggested that magnesium sulfate slows gastrointestinal function and may lead to respiratory suppression. Last, a Cochrane review of seven studies in 2002 found an increased risk for perinatal death with prenatal exposure to magnesium; however, a more recent systematic review showed no increase in fetal or neonatal death before discharge for magnesium compared with any alternative tocolytic regimen or control group.

Despite potential adverse neonatal effects, contrary evidence has suggested that prenatal exposure to magnesium may have a neuroprotective benefit. A randomized, controlled trial by Crowther and associates evaluating the neuroprotective effect of magnesium given before preterm birth found an almost a 50% reduction in gross motor dysfunction (3.4% vs 6.6%) in the group treated with magnesium sulfate compared with placebo. These findings were supported by Marret and co-workers, who demonstrated a reduction in death or motor/cognitive dysfunction among the group receiving magnesium sulfate. In 2008, a randomized controlled trial by Rouse and colleagues examined the role of magnesium sulfate for the prevention of cerebral palsy in 2241 patients. The study was conducted among women at gestational ages of 24 to 31 6/7 weeks who received a standard 6-g loading dose followed by a continuous infusion of 2g/h until the time of delivery. The study showed a 45% reduction in the overall rate of cerebral palsy (4.2% vs 7.3%) and in moderate or severe cerebral palsy (1.9% vs 3.5%) in the infants receiving magnesium.

Although it is widely used as a tocolytic agent, the literature does not support magnesium sulfate as being effective in withholding delivery for 48 hours, preventing preterm birth, or reducing the risk for neonatal morbidity. Given its association with the reduction in the rate of cerebral palsy, magnesium’s best role seems to be as a neuroprotective agent for the fetus.

BETA-MIMETICS

The role of beta-mimetics for tocolysis has been explored since the 1970s. Medications belonging to this class include terbutaline (Brethine), ritodrine (Yutopar), salbutamol, and hexoprenaline. Ritodrine is the only Food and Drug Administration-approved tocolytic medication, but it is no longer available in the United States. Although beta-mimetics were initially commonly used, they have fallen out of favor secondary to their maternal and fetal side effects and a recent warning released in February 2011 by the US Food and Drug Administration. The US Food and Drug Administration placed a boxed warning on the drug’s label stating that the medication should not be used for prolonged tocolysis (>48–72 hours) because of the potential for serious maternal cardiac toxicity and death.

Beta-mimetics function as beta-adrenergic receptor agonists, relaxing smooth muscles, including the myometrium. Binding of the receptor activates a cascade of
intracellular reactions that affect adenyl cyclase and protein kinase. This cascade decreases the availability of intracellular calcium and the activity of myosin light-chain kinases, thus suppressing myometrial contractility.

The efficacy of beta-mimetics as a tocolytic has predominately involved studies that compared ritodrine with another tocolytic agent or placebo. In a Cochrane meta-analysis of 11 randomized trials of beta-mimetics versus placebo for preterm labor, beta-mimetics decreased the risk of delivery within 48 hours and showed a trend toward reduction in delivery within 7 days, but there was no reduction in preterm birth or neonatal morbidity. Based on the available literature, beta-mimetics do not seem to be a superior tocolytic than other medications. When beta-mimetics were compared with nifedipine in a large meta-analysis of 16 trials, beta-mimetics were not as effective as nifedipine in reducing the risk of delivery within 7 days or before 34 weeks gestation. They were also less effective at reducing the risk for neonatal respiratory distress syndrome. In another review of 5 studies comparing beta-mimetics with magnesium sulfate, beta-mimetics were not associated with reducing delivery at any interval (within 48 hours, 7 days, or before 37 weeks) or in reducing low birth weight infants.

Terbutaline is the most commonly used beta-mimetic for preterm labor in the United States and it is generally administered as a subcutaneous injection. Given its off-label use, the dosing may vary, but, most commonly, 0.25 mg is given subcutaneously and may be repeated in 15 to 30 minutes if there is inadequate response. Total dosing in 4 hours should not exceed 0.5 mg. Common maternal side effects secondary to beta-mimetics include tachycardia, tremor, dyspnea, chest discomfort, palpitations, and hyperglycemia. These side effects may be unpleasant to the patient and often result in discontinuation of treatment. More rare side effects include pulmonary edema and myocardial ischemia, but these may be related to other confounding factors, like fluid overload, infection, preeclampsia, or underlying cardiac disease. With prolonged use of beta-mimetics, tachyphylaxis may develop.

Given the known side effects, this class of medication is contraindicated in patients with known cardiac disease or poorly controlled diabetes. It should be withheld if maternal heart rate increases to more than 120 beats/minute or the patient experiences significant symptoms such as dyspnea or chest pain.

Beta-mimetics cross the placental barrier and may lead to fetal effects. Side effects include fetal tachycardia in response to maternal tachycardia and neonatal hypoglycemia linked to maternal hyperglycemia. In addition, question has been raised linking beta-mimetics to an increased risk of neonatal intraventricular hemorrhage, although this has been refuted in other studies.

**CALCium CHANNEL BLOCKERS**

Calcium channel blockers are typically used in the treatment of hypertension, angina, and coronary artery disease and exert their effect by preventing reuptake of calcium ions via the voltage-dependent calcium channels. The resultant decrease in intracellular calcium leads to inhibition of actin and myosin interaction and, therefore, decreased myometrial contractility. Given their ability to relax smooth muscle, calcium channel blockers, in particular nifedipine, are widely used tocolytic agents.

A recent systematic review and meta-analysis of 26 randomized, controlled trials evaluated nifedipine (Procardia) compared with other tocolytics, placebo, or no treatment in the management of preterm labor. To date, no placebo-controlled trials of nifedipine have been published. When compared with beta-mimetics, nifedipine showed a significant reduction in the risk of delivery within 7 days of initiation of treatment (37% vs 45%) as well as a reduction in rate of delivery before 34 weeks
When nifedipine was compared with magnesium sulfate, there was no overall difference in delivery within 48 hours or before 34 or 37 weeks’ gestation. This meta-analysis also revealed a significant improvement in neonatal outcomes with nifedipine tocolysis including a reduction in the rate of the common neonatal morbidities of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. Nifedipine was also associated with fewer NICU admissions and shorter NICU stays.

There are numerous dosing regimens for tocolysis with nifedipine discussed in the literature with most using oral capsules. Initial loading doses range from 10 to 40 mg followed by 10 to 20 mg every 4 to 6 hours, with the dose titrated based on contraction pattern. Nifedipine is usually well-tolerated with minimal cardiovascular alterations. In a meta-analysis, nifedipine was less likely to result in maternal side effects when compared with other tocolytics such as beta-mimetics or magnesium sulfate. The majority of maternal side effects with nifedipine are related to relaxation of endothelial smooth muscle, which leads to peripheral vasodilation. Maternal symptoms often include nausea, flushing, headache, dizziness, and palpitations. Peripheral vasodilation leads to a compensatory rise in heart rate and stroke volume which increases cardiac output, allowing for maintenance of blood pressure in women with no underlying cardiovascular disease. Rare but more serious maternal side effects include pulmonary edema, hypoxia, myocardial infarction, atrial fibrillation, and severe hypotension. Calcium channel blockers should be used with caution in conjunction with magnesium sulfate as cases of cardiovascular collapse have been reported.

The fetal effects of calcium channel blockers are related to its peripheral vasodilative effects and risk of maternal hypotension which can lead to hypoperfusion of the uterus and placenta. Therefore, monitoring of maternal blood pressure and avoidance of calcium channel blockers in women at high risk for hypotension (cardiovascular disease, multiple gestations) are recommended.

PROSTAGLANDIN INHIBITORS

Indomethacin (Indocin), a nonselective COX inhibitor, is the most widely used prostaglandin inhibitor to treat preterm labor. Prostaglandins are known to play a crucial role in the onset of labor through the formation of gap junctions in the myometrium that increase intracellular calcium and facilitate myometrial contractility. Prostaglandin inhibitors function as tocolytics through inhibition of the COX enzyme responsible for converting arachidonic acid to prostaglandins.

Indomethacin has been shown to be an effective tocolytic agent. In addition, it is easy to administer, inexpensive, and has minimal maternal side effects. A 2005 Cochrane review of COX inhibitors for treating preterm labor evaluated 13 trials with a total of 713 women. Indomethacin was shown to be effective when compared with placebo at reducing preterm birth before 37 weeks in 1 trial that included 36 women. In addition, there was a significant increase in gestational age by 3.5 weeks and birth weight of 716 g in 2 trials of 67 women compared with placebo. Despite these findings, there was no difference in perinatal mortality or morbidity, including respiratory distress syndrome or intraventricular hemorrhage. In this same review, 3 trials of 168 women evaluated indomethacin compared with other tocolytic agents, including beta-mimetics and magnesium sulfate. A similar reduction in preterm birth before 37 weeks was seen without any difference in overall perinatal mortality. Selective COX-2 inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx) have also been compared with indomethacin with no appreciated difference in maternal or neonatal outcomes.
For tocolytic therapy, indomethacin is generally administered as a loading dose of 50 to 100 mg orally or 50 mg rectally followed by 25 to 50 mg every 6 hours for 48 hours. Maternal side effects are primarily related to the gastrointestinal tract and include nausea, vomiting, gastroesophageal reflux, and gastritis. In addition, platelet dysfunction may occur with use of prostaglandin inhibitors. Selective COX-2 inhibitors have fewer gastrointestinal side effects; however, they are associated with increased cardiovascular risks and, therefore, should be used with caution. Overall, studies have shown that prostaglandin inhibitors are better tolerated and have a lower discontinuation rate owing to side effects than other tocolytics such as beta-mimetics and magnesium sulfate.

The usefulness of prostaglandin inhibitors as tocolytics is limited by their effects on the fetus, primarily premature closure of the ductus arteriosus and oligohydramnios. Long-term use of indomethacin is associated with premature closure of the ductus arteriosus in 25% to 50% of pregnancies and results in oligohydramnios in 5% to 70% of pregnancies. A retrospective study of 124 women receiving prolonged indomethacin (≥48 hours) reported the incidence of ductal constriction to be less than previously reported at 6.5% with reversal of constriction 24 to 48 hours after discontinuation of therapy. In addition, the incidence of ductal constriction is reported to be dependent on gestational age at the time of use with increased risk of premature closure at later gestational ages (>31 weeks). When used for a short duration (<48 hours), the incidence of oligohydramnios is low. In a study of 61 women before 34 weeks’ gestation, the incidence of oligohydramnios was only 3.3% with return to normal amniotic fluid volume within 24 hours of discontinuation. Indomethacin has been linked to other adverse neonatal outcomes, including necrotizing enterocolitis, intraventricular hemorrhage, and cardiac, pulmonary, and renal abnormalities, although these associations were not supported in a more recent meta-analysis of randomized and observational studies. Although concern for fetal side effects of indomethacin may limit prolonged use, it seems to be a safe and effective tocolytic when used for a short period of time.

**OXYTOCIN RECEPTOR ANTAGONIST**

Given the overall limited efficacy of traditional tocolytic therapy, many European nations have explored the use of an oxytocin receptor antagonist atosiban (Tractocile). Atosiban, in theory, should have limited systemic maternal effects because of its site-specific action on myometrial cells in the uterus and myoepithelial cells in mammary glands, the only known locations of oxytocin receptor expression. Atosiban is a synthetic peptide that functions by blocking oxytocin from binding to its receptor and by downregulating the number of oxytocin receptors, thus decreasing myometrial contractility.

Like other tocolytics, there is uncertainty about the efficacy of atosiban as a first-line tocolytic agent. In a meta-analysis that included 2 randomized, controlled trials that compared atosiban with placebo, a small but significant increase in women undelivered at 48 hours was seen in the atosiban group. This result, however, was not seen in a 2005 Cochrane Review of oxytocin receptor antagonists for inhibiting preterm labor. Atosiban was not shown to delay delivery for 48 hours, prevent preterm birth, or improve neonatal outcomes. Atosiban has also not been shown to be superior to other tocolytics. Two small studies have compared atosiban and nifedipine and did not show a difference in efficacy between the 2 medications. Given their limited sample sizes, a larger randomized study would be necessary to better compare treatment superiority. Atosiban has been compared with beta-mimetics in
large, randomized, controlled trials in Europe, with no difference in tocolytic effectiveness at 48 hours or 7 days or in neonatal outcomes.\textsuperscript{56,57}

Atosiban is administered as a continuous intravenous infusion with a loading dose of 6.75 mg followed by a maintenance dose of 300 $\mu$g/min for 3 hours, and then 100 $\mu$g/min for up to 48 hours.\textsuperscript{57}

Studies of atosiban show limited side effects on both mother and fetus. When administered intravenously, it achieves a rapid maternal plasma steady state followed by a high clearance rate, with an estimated half-life of 18 minutes.\textsuperscript{58} In addition, studies suggest that atosiban crosses the placenta in a limited fashion and does not seem to accumulate in the fetal circulation.\textsuperscript{59} Unlike some tocolytics, atosiban does not alter maternal or fetal cardiovascular parameters in animal models, making it a very tolerable drug.\textsuperscript{60} The most commonly cited maternal adverse reactions to atosiban include headache, nausea, and vomiting (8\%–12\%).\textsuperscript{61} These adverse effects are more common during the loading period of the drug and decrease significantly during the maintenance period of the infusion.\textsuperscript{62} In terms of overall maternal side effects, studies comparing atosiban with nifedipine and beta-mimetics favor atosiban.\textsuperscript{54–56,61}

Questions have been raised about higher rates of death among infants exposed to atosiban. In a study by Romero and colleagues\textsuperscript{63} that included 583 infants, more women were unexpectedly randomly allocated to receive atosiban as opposed to placebo before 26 weeks’ gestation (10\% vs 5\%). There were more fetal–infant deaths in the group receiving atosiban (4.5\% vs 1.7\%). Seven of the 10 infant deaths in the atosiban group were among babies weighing less than 650 g; therefore, extreme prematurity may have played a significant role in the adverse neonatal outcomes in this group.\textsuperscript{63,64} Given the increased infant deaths in the atosiban group, the US Food and Drug Administration has not approved the use of this drug for tocolysis in the United States.\textsuperscript{30}

**SUMMARY**

The pathophysiology leading to preterm labor is not well understood and often multifactorial; initiating factors include intrauterine infection, inflammation, ischemia, overdistension, and hemorrhage.\textsuperscript{3} Given these different potential causes, directing therapy for preterm labor has been difficult and suboptimal. To date, no single drug has been identified as successful in treating all of the underlying mechanisms leading to preterm labor. In addition, the methodology of many of the tocolytic studies is limited by lack of sufficient patient numbers, lack of comparison with a placebo, and inconsistent use of glucocorticoids. The limitations in these individual studies make it difficult to evaluate the efficacy of a single tocolytic by meta-analysis. Despite these limitations, the goals for tocolysis for preterm labor are clear: To complete a course of glucocorticoids and secure the appropriate level of neonatal care for the fetus in the event of preterm delivery.

The literature demonstrates that many tocolytic agents inhibit uterine contractility. The decision as to which tocolytic agent should be used as first-line therapy for a patient is based on multiple factors, including gestational age, the patient’s medical history, common and severe side effects, and a patient’s response to therapy. In a patient at less than 32 weeks gestation, indomethacin may be a reasonable first choice based on its efficacy, ease of administration, and minimal side effects. Concurrent administration of magnesium for neuroprotection may be given. At 32 to 34 weeks, nifedipine may be a reasonable first choice because it does not carry the fetal risks of indomethacin at these later gestational ages, is easy to administer, and has limited side effects relative to beta-mimetics.
In an effort to review a commonly faced obstetrical complication, this article has provided a summary of the most commonly used tocolytics, their mechanisms of action, side effects, and clinical data regarding their efficacy.

REFERENCES


