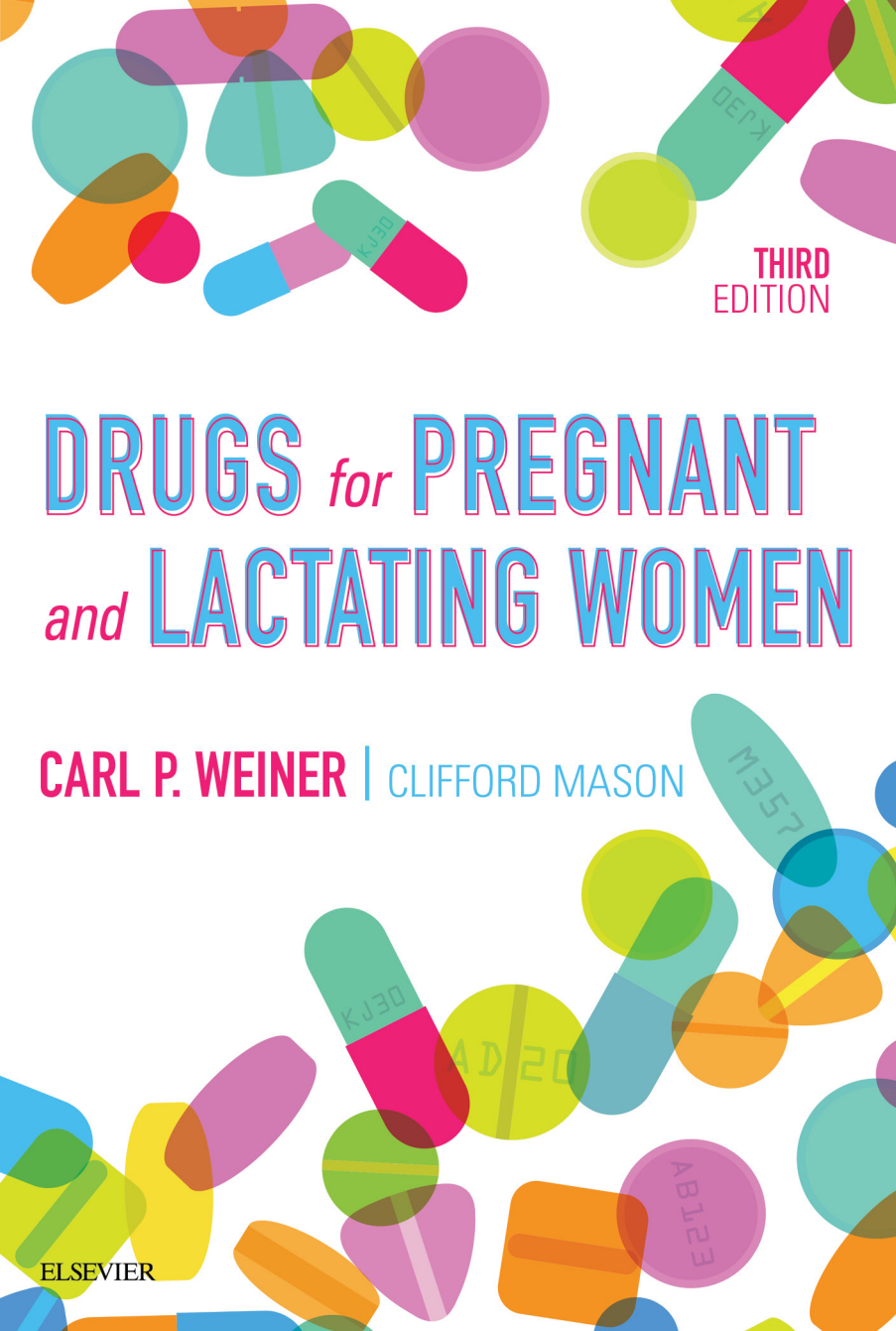
THIRD
EDITION
DRUGS for PREGNANT
and LACTATING WOMEN
CARL P. WEINER | CLIFFORD MASON
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THIRD
EDITION

DRUGS *for* PREGNANT *and* LACTATING WOMEN

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Foreword to the Second Edition

This is a dream come true for all of those who care for pregnant and nonpregnant women. There is nothing like this in medical literature. In the past, I have been involved in the publications of several texts on drugs and pregnancy. This new text is on the leading edge of science and knowledge for women and drugs, with more than 720 generic drugs with their 1500 trade names listed in alphabetical order to make identification easy for each drug. Over-the-counter drugs are also included. The information provided in both hard text and electronic versions is very extensive, concise, and user friendly. Its availability as an electronic version for hand-held computer devices, that will be updated for the life of the edition, is particularly exciting. This will not only benefit all health care workers in the field of obstetrics and gynecology, but will also allow instantaneous access to drug related questions.

Included in text and electronic versions are the following headings:

Name
Class
Indications
Dosage with qualifiers
Maternal Considerations
Fetal Considerations
Breastfeeding Safety
References
Summary

Also included are lists of known teratogens, pregnancy drug registries, AHA endocarditis guidelines, FDA category definitions, and the percent of drugs assigned to them.

Thanks go to Dr. Weiner for his ingenuity in taking a complicated problem and making it straightforward and simple for those who care for pregnant and nonpregnant women.

This effort is the first to simultaneously embrace text and an electronic version for hand-held computers. The combination of Elsevier—the world's largest health sciences publisher—and Dr. Weiner—an individual who has a long-term interest in female reproduction and especially high-risk obstetrics—assures success of the project.

This is the new frontier in medical publishing, and we will look forward to additions and revisions in the electronic format.

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Foreword to the First Edition

The study of medication use in pregnancy is one of the least developed and most neglected areas of clinical pharmacology and drug research. Although pregnancy is widely regarded as a special population due to both the unique maternal physiology and the vulnerability of the developing fetus, researchers and pharmaceutical companies have been reticent to evaluate optimal modalities of treatment for this group. The issue is compounded by the enormous number of medications women are exposed to during pregnancy. Epidemiological surveys indicate nearly two thirds of all pregnant women use four to five drugs during pregnancy through delivery. Women with medical conditions such as epilepsy, diabetes, and hypertension must continue therapy while pregnant. In some cases, due to a justified or unjustified concern for the developing fetus, the medication prescribed is either withheld, inadequate to treat the maternal condition, or not monitored closely enough as pregnancy progresses for needed adjustments in dosing. The result is a double negative, that of fetal exposure without maternal or fetal benefit. The lack of Food and Drug Administration obstetric labeling and the near universal off-label use of drugs are the direct result of the paucity of research and clinical trials in this special population. The public concern stems from the use of drugs in pregnancy based on an empiric approach rather than a scientific basis, and does not take into account the many alterations in pregnancy.

There are profound physiologic changes in pregnancy involving the mother, placenta and fetus that may alter absorption, distribution and elimination of drugs. For example, there is a decrease in gastric emptying and an increase in intestinal transit time, both of which may alter gastrointestinal absorption of drugs. Similarly, the physiologic increase in pulmonary blood flow, hyperventilation, or increased tidal volume during pregnancy may increase the absorption of inhalants. The dramatic increase in blood volume with subsequent dilutional hypoalbuminemia, especially in the third trimester, can be associated with a decreased drug binding capacity and may profoundly affect the distribution of many drugs during pregnancy. These are but a few of the many examples of the complex changes in pregnancy that affect the type, dosing, and effectiveness of medications in this special population.

Daily advances in therapeutics dramatically increase the number and types of medications available more rapidly than textbooks can be updated. This new text by Weiner and Buhimschi, *Drugs for Pregnant and Lactating Women*, helps fill the void. It is a comprehensive resource addressing the unique needs of this special population. Each drug entry includes the generic and trade names, drug class, indication(s) (on and off label), mechanism(s) of action, dosage, maternal and fetal considerations, breastfeeding safety, references, FDA pregnancy and lactation categories, and a summary. Wherever possible, evidence- based recommendations are made. This unique reference combines the printed word with an electronic version updated quarterly to allow for the incorporation of the new therapeutics. This design is user friendly for the busy clinician and includes prescribing information as well as a review of the published experience with the drug in pregnancy and lactation. As the first of its type, *Drugs for Pregnant and Lactating Women* will simplify the clinician's ability to maintain updated information on medications in pregnancy and facilitate the incorporation of more rigorous study into the use of medications in the pregnant and lactating populations.

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Preface

Millions of pregnant and breast-feeding women take a prescription and or an over-the-counter drug daily. Since the publication of our first edition 14 years ago, our knowledge base has increased steadily, especially when it comes to breastfeeding. Slowly, dogma is being replaced with fact. Most medications are safe, but every year a small percentage will have unintended adverse consequences for either mother or child. Sometimes, new information emerges about a well known and commonly used medication such as ondansetron popular for the treatment of nausea and vomiting of pregnancy. An additional percentage of drugs administered prove ineffective, due in part to the unique physiology of pregnancy or breastfeeding. And while an unnecessary drug should never be given to the pregnant or breast-feeding woman, an important therapy should never be withheld because of her status.

Health care givers are accustomed to routinely checking the FDA classification of a drug before prescribing it. Unfortunately, this classification system, while simple in concept, is outdated, rarely revised as new information becomes available, and too simplistic to account for the physiology and health care needs of pregnant and breast-feeding women. Few drugs are approved by the FDA for use during pregnancy, and even oxytocin is a Category X agent. The important information provided by the manufacturer is often couched in protective legalese and never focuses on the needs of the obstetrical health care provider. Prior reference books proved dense and were filled with descriptions of animal studies but not their implications. As a result, they are used in practice as a source of the FDA pregnancy category.

So much has changed since the publication of the first edition, and I would like to thank the many health care providers who provided valuable feedback now incorporated into the third edition. A number of other texts have attempted to mimic our layout, and since imitation is the best form of flattery, we thank them for their acknowledgment of the great utility of our book. In addition to the several hundred new drugs added since the first publication, we have attempted in the third edition to further enhance relevant Drug Interactions. The text continues its user friendly format available in both electronic and hard copy media.

The purpose of the third edition remains to provide a user friendly, pregnancy-lactation–focused reference for the use of the concerned health care provider. Do not use this as a reference when prescribing for a man. Although we recommend consulting a more complete reference before prescribing an unfamiliar agent, the information provided will aid the safe prescribing of drugs familiar to the physician. The number of new drugs released grows yearly, and their known impact on pregnancy and lactation, and vice versa, is often limited to absent. Conflicts in FDA class with existing knowledge are pointed out, and recommendations are made wherever possible based on medical evidence. The FDA has embarqued on a new and more detailed classification of drug safety during pregnancy.

Still in its early days, I have attempted to include this information wherever possible.

Carl P. Weiner

Acknowledgments

For the third edition, I was joined by a new writing partner, a pharmacologist, Dr. Clifford Mason. His help was indispensible.

I also want to recognize Kate Rope, my co-author on a companion book for patients, *The Complete Guide to Medications During Pregnancy and Lactation*, St. Martin's Press, 2013. I believe the blending of the two projects made both of them better.

Carl P. Weiner

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Introduction

Frustrated by the absence of a comprehensive resource that recognizes the uniqueness of medical needs during pregnancy and lactation, we created *Drugs for Pregnant and Lactating Women* as an easy-to-use, reader friendly resource containing the key information required by caregivers to make prescribing decisions. Too often, we check only the FDA Pregnancy Category before making a decision to prescribe or discontinue a medication. Unfortunately, few of us have read these definitions (TABLE 1), understand their limitations, and realize the assigned category is essentially stagnant, based predominantly on information available when the drug was approved in the United States, and only occasionally officially updated to reflect advancing knowledge. Two-thirds of all drugs sold in the United States are classified Category C, and less than 1% are Category A. With the benefit of added experience, we learn that many Category X drugs are not absolutely contraindicated during pregnancy, and several Category C or D drugs are either clear human teratogens or have frequent and serious adverse fetal effects. These facts are highlighted by a study comparing the categorization of same drugs by the appropriate agencies in the United States, Australia, and Sweden (Addis A, Sharabi S, Bonati M. Drug Saf 2000; 23:245-53). Only 25% of the 236 drugs common to all three systems were placed into the same risk factor category. Nor does the categorization inform the provider how either pregnancy or lactation may alter the patient's response to therapy compared to the nonpregnant state. The FDA is well aware of these limitations and is actively considering revision. Lastly, increasingly busy health care providers are often dependent on either the advertisements in trade journals or the pharmaceutical house detail people for up-to-date information on new drugs. Yet, a recent study observed that promotional claims are frequently misleading, and the cited studies were either unretrievable or failed to back up the particular claim (Villanueva P, Peiro S, Libero J, Pereiro I. Lancet 2003; 361:27-32). This is not a new problem (Wilkes MS, Doblin B, Shapiro M. Ann Intern Med 1992; 116:912-19).

This text seeks to reduce the aforenoted limitations by using brief descriptions to summarize the current level of knowledge. New for the third edition, the information on each drug is divided into 12 sections. Those who purchase the electronic version can search by subgroups or names in each of these sections.

The first section of the text lists the generic Name followed by trade names used in the United States. Some drugs have a half dozen or more trade names and are difficult to remember if you do not use them regularly.

Also in the third edition, the second section lists the common International Trade Names. It is our intent this be an international resource for obstetric caregivers.

The third section is the drug Class, such as antibiotic (type), nonsteroidal antiinflammatory (NSAID), anticonvulsant, antihypertensive, etc. This makes it easier to sort drugs in search of alternative or complementary agents when necessary.

The fourth section lists the Indications for the drug. In most, though not all instances, this list is confined to FDA-approved indications. Popular off-label uses are typically reviewed in a subsequent section.

The fifth section is the known or presumed Mechanism of Action. This is frequently unknown, or if several activities of the drug are known, it is unclear whether they are responsible for the disease-directed action of the drug. Knowledge of the mechanism of action is important for the selection of complementary drugs and the prediction of adverse effects.

The sixth section contains the Dose by specific indication. Also included in this section are most relevant Contraindications and Cautions. This information is mostly derived from manufacturer-provided material but tailored for women. You will not find erectile dysfunction or benign prostatic hypertrophy as either an indication or a contraindication for a particular drug, although they certainly might be listed in a general drug text. Also frequently removed from the list are typical corporate liability comments on pregnancy that are not substantiated by either animal or human experience. The dose advice provided has been checked multiple times by at least three individuals. However, the very design of this text assumes the prescriber has previously familiarized himself or herself with the contents of the package insert. The details provided under Dose are a suitable refresher but not a substitute. We strongly recommend that you confirm the dose when using an unfamiliar drug. Furthermore, we have adopted the approach of simply noting when a dose modification must be considered, rather than trying to be all things for all situations. The standard “NOTE” mentions the need for either renal or hepatic dosing. This means that, in the face of compromised renal or hepatic function, the physician must take into account altered clearance of the drug. The formulas are usually contained in the package insert or may be discussed with the dispensing pharmacist.

The seventh and eighth sections form the unique core of the text. In the seventh, titled Maternal Considerations, we review how the drug impacts pregnancy and vice versa. We summarize the published experience during pregnancy, highlighting any known problems. Off-label uses are detailed, as is the evidence for efficacy if it exists. We also note applications that have proved unsuccessful. The sad reality is that many drugs used during pregnancy are either ineffective or poorly effective for their most common uses—the tocolytic agents being prime examples. Specific evidence-based recommendations are made wherever possible. It is in this section we also detail the known drug Side

Effects, again focusing on mother and child. Priapism and impotence may be important side effects in some populations but not in the one for which our envisioned reader provides care.

The eighth section is titled Fetal Considerations. Here, the impact of the drug on the human fetus is reviewed, information on placental transfer presented (e.g., the fetal umbilical vein: maternal vein ratio), and any adverse effects summarized. The possible applications of a drug for fetal therapy and an appraisal of its efficacy will also be found here. Animal data are presented when human experience is missing. Rodent teratogenicity studies are summarized, where available, recognizing there are well-known human teratogens, which were not teratogens in rodents (e.g., thalidomide). Of potential relevance is the dose at which the adverse effects are seen in rodents (in terms of multiples of the maximum recommended human dose), and the presence or absence of maternal toxicity that may be the proximate cause of the noted effect. Much of this information is published in peer-reviewed articles, but in some instances, the only source of this information is the manufacturer. It is frightening to us, as practitioners, to find how little is known about many commonly used drugs during pregnancy and lactation. It is our hope readers will be encouraged when confronted with the facts to try and fill in the missing information with quality studies. The number of drugs withheld from women during pregnancy or lactation because of unsubstantiated or, at times, past but refuted theories is of at least equal concern.

New for the third edition, the ninth section is entitled Drug Interactions. Here, the more common or dangerous drug:drug interactions are noted. This is an ever-growing risk in this era of polypharmacy.

The tenth section is Breastfeeding. We note whether the drug enters human breast milk and the kinetics of its excretion, if known. The ideal information includes the weight-corrected percent of the maternal dose ingested by the unsupplemented 3kg-newborn and the resulting neonatal blood levels. The number of times the ideal is achieved can be counted on the hands of a single individual. When this information is not known, a milk:plasma (M:P) ratio or concentration is given. This information provides limited information and may indeed mislead the reader. When no human data are available, animal (typically rodent) is proffered, wherever available. Some of this information is published in peer-reviewed articles and some by the manufacturer. Occasional conflicts are noted, and wherever possible, specific evidence-based recommendations made. For example, many drugs are used for a limited period or even one-time use. When the patient wishes to continue breastfeeding, but there is reasonable doubt of safety, we will recommend the patient pump her breasts for a period of time before resuming breastfeeding. In other instances, the drug may be safe but not the mother if, for example, the woman has HIV.

Section eleven contains salient References. Most are directed at source material, but some are reviews. This information is rarely in packaged inserts (which comprise, for example, the *Physicians Desk Reference*) and cover maternal, fetal, and lactational issues.

The final section, section twelve, is entitled Summary. In this section, the reader will find the FDA category as published in the package insert and a code assigned by the editors for breast-feeding safety (S, safe; NS, not safe; and U, unknown). Often there is some but not enough information for a particular conclusion. In these situations, we have placed a question mark next to the selected code (e.g., S?). The final comments always reflect the need to balance risk. This is a patient-specific process and not given to absolutes. In many instances, the reader is informed that there are other alternatives that include more experience in pregnancy and lactation. We strongly suggest that wherever possible, the reader seek and use those agents. Pregnancy is not the occasion to be a pioneer, if unnecessary. If there is a post-marketing registry, the telephone number is listed in the Appendix. These registries have the potential to identify important but unusual outcomes.

This text has always been designed as a living resource. New print editions will be frequent, and those readers with the electronic version will receive periodic updates when they re-synchronize their hand-held computers. There are already several hundred new drugs in the third compared to the first and second editions, and all have been subject in the third edition to a literature search. Also new is a growing number of popular herbal remedies with which the obstetrical caregiver will be confronted during the normal course of practice. Readers are encouraged to contact the editors with comments, concerns, and criticisms.

Carl P. Weiner

Contents

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Acarbose — (Precose)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class

α-Glucosidase inhibitor; Antidiabetic agents; Oral hypoglycemics

Indications

Diabetes mellitus, type 2

Mechanism

An oral pancreatic α-amylase and intestinal α-glucoside hydrolase inhibitor that delays bowel carbohydrate metabolism, slowing the postprandial rise in glucose

Dosage With Qualifiers

Diabetes mellitus, type 2—begin 25 mg (50 mg if >60 kg); thereafter, 50–100 mg PO ac tid based on glucose levels

- **Contraindications**—hypersensitivity to drug or class, DKA, cirrhosis, intestinal obstruction or malabsorption syndromes
- **Caution**—renal dysfunction

Maternal Considerations

Acarbose has been shown to reduce/delay the onset of type 2 diabetes in patients with impaired glucose intolerance. There are no adequate reports or well-controlled studies of **acarbose** in pregnant women. Two studies of pregnant women with impaired glucose tolerance compare **acarbose to other oral hypoglycemic agents**. **Acarbose** produced outcomes as good or superior to insulin and glyburide.
Side effects include intestinal discomfort consisting of pain, diarrhea, flatulence, elevated LFTs, and jaundice.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Only 2% of the oral dose is absorbed. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses almost 10× higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **acarbose** enters human breast milk. However, < 2% of **acarbose** is bioavailable. It is unlikely any would be excreted into the milk and/or absorbed by the neonate. The drug and/or its metabolites have been found in the milk of lactating rats at levels reaching 10 times the maternal plasma levels. A single rat study suggests **acarbose** might alter the composition of breast milk by inhibiting lipogenesis.

Drug Interactions

Some drugs such as thiazides (and similar class diuretics), corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, **phenytoin**, **nicotinic acid,** sympathomimetics, calcium channel blocking drugs, and **isoniazid** can cause hyperglycemia. Women taking both **acarbose** and one of these drugs should be monitored closely for loss of glucose control. Discontinuation of such drugs may lead to hypoglycemia.
Intestinal adsorbents (e.g., charcoal) and digestive enzyme such as **amylase** and **pancreatin** may reduce the effect of **acarbose** and should not be taken together.
Acarbose may alter **digoxin** bioavailability when they are co-administered.
Neomycin may decrease acarbose metabolism.
Quinolone antibiotics, SSRIs, salicylates, and MAO inhibitors may enhance the hypoglycemic effect of acarbose and other blood glucose lowering agents.

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Summary

Pregnancy Category: B
Lactation Category: S (likely)

- Insulin and diet regulation remain the standard treatments for glucose intolerance during pregnancy.
- There is a growing interest in the use of oral hypoglycemic agents during pregnancy, and **acarbose** is an interesting candidate.

Acetaminophen — (APAP; Acephen; Aceta; Acetaminophen Uniserts; Anapark; Apacet; Asidon; Calip; Dapacin; Ed-Apap; Feverall; Genapap; Genebs; Mapap; Maranox; Neopap; Oraphen-PD; Panadol; Redutemp; Ridenol; Silapap; Tapanol; Tempra; Tylenol; Uni-Ace)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Analgesics, non-narcotic; Antipyretics; NSAID
Indications	Mild pain, fever, menstrual cramps, osteoarthritis, tension headache
Mechanism	Nonspecific cyclooxygenase inhibitor
Dosage With Qualifiers	Pain and/or fever—650–1000 mg PO/PR q4–6 h; max 4 g/d *NOTE: Included in many combinations.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction, chronic alcohol use, G6PD deficiency, PKU
Maternal Considerations	**Acetaminophen** is a component of a long list of OTC medications and is used by 40%–70% of pregnant women. It is metabolized in the liver and excreted by the kidneys. During the first trimester, the mean t/2 is significantly lower and oral clearance is significantly higher compared to nonpregnant control subjects. Only during pregnancy is weight related to clearance, suggesting the dose may need to be adjusted in obese women. **Ibuprofen** provides more rapid relief of perineal pain after vaginal delivery. In one RCT, **acetaminophen** plus **oxycodone** was superior to patient-controlled **morphine** for the relief of postcesarean pain. There are no obvious differences in clearance at term. Chronic abuse and overdose are the most common problems. The damage appears secondary to free radical toxicity with consumption of glutathione. ***N*-acetylcysteine** is the treatment of choice for acute overdose. In one prospective case-control study, use of prenatal **ibuprofen, naproxen,** and **aspirin,** but not **acetaminophen,** increased the risk of spontaneous abortion by 80% (adjusted hazard ratio 1.8 [95% CI 1.0–3.2]). The association was stronger if the initial use occurred around conception or if the use lasted more than a week. **Acetaminophen** may interfere with sex and thyroid hormone function. Human trials reveal a correlation between **acetaminophen** use during pregnancy and increased risk for childhood wheezing and asthma. ***Side effects*** include hepatotoxicity, nephrotoxicity, agranulocytosis, pancytopenia, hemolytic anemia, pancreatitis, rash, angioedema, and urticaria.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Acetaminophen** crosses the human placenta, reaching steady state in the isolated perfused model within 1 h. The F:M ratio for **acetaminophen** approximated 0.12 in the pregnant ewe, and neither sulfate nor glucuronide metabolites crossed. **Acetaminophen** use during labor to treat the fever of chorioamnionitis is associated with improved fetal umbilical blood gases, presumably by reducing fetal oxygen demand as the maternal core temperature declines. Although it was previously suggested that exposure to **acetaminophen** was associated with clubfoot and digital abnormalities, these reports are not sustained in large series. Unlike aspirin, **acetaminophen** has no antiplatelet activity and does not pose a hemorrhagic risk to the fetus. There does appear to be a link between **acetaminophen** and gastroschisis/small bowel atresia. Two studies based on population-level trends suggest **acetaminophen** use is associated with the incidence/prevalence of autism. One large prospective observational study concluded that the use of **acetaminophen** (especially when the exposure was 28 d or more) was associated with motor milestone delay, gross and fine motor impairment, communication impairment, impairments in internalizing and externalizing behaviors, and hyperactivity. Two other large cohort studies based on the Danish National Birth cohort are especially concerning. In the first, **acetaminophen** use during pregnancy is associated with an increased risk of autism spectrum disorder, but only when a hyperkinetic disorder was also present. This report was recently confirmed in a UK study. In the second Danish National cohort report, **acetaminophen** use in the first and second trimesters had a negative impact on IQ at age 5 y when taken for pain or inflammation, but not fever. Fever alone had a negative impact on IQ at age 5 y, and **acetaminophen** use for fever eliminated the effect of fever.
Breastfeeding Safety	**Acetaminophen** is excreted in low concentrations into breast milk. The amount of the drug administered to the mother estimated to be available to the neonate ranges from 0.04% to 0.23%, and it is generally considered compatible with breastfeeding.

Drug Interactions

Tramadol may increase the risk of **acetaminophen** toxicity.
Local anesthetics may increase the risk of methemoglobinemia.
Excessive use of acetaminophen and alcohol increases risk of hepatotoxicity.
There is an increased risk of acetaminophen hepatotoxicity if used with barbiturates, carbamazepine, hydantoins, and sulfinpyrazone.

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Summary

Pregnancy Category: B (?)
Lactation Category: S

- **Acetaminophen** has been used throughout pregnancy for analgesia and to reduce fever.
- Though generally considered safe for use during pregnancy, human studies consistently raise concern that **acetaminophen** may be associated with either ADHD or autism. And although it may offset the impact of maternal fever on child IQ at age 5 y, **acetaminophen** used for other indications in the first and second trimesters may negatively affect the child's IQ at age 5 y. Caution is warranted.
- Like most drugs, it should be used during the first and second trimesters only when clearly necessary.

Acetazolamide — (Acetadiazol; Acetamide; Azomid; Dehydratin; Diamox; Diamox Sequels; Diamox Sodium; Ederen; Glauconox; Inidrase; Nephramid; Oratrol)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class

Carbonic anhydrase inhibitors; Diuretics

Indications

Glaucoma, open and closed angle; altitude sickness, prevention and treatment; epilepsy; CHF; drug-induced edema; urinary alkalinization

Mechanism

Carbonic anhydrase inhibitor

Dosage With Qualifiers

Glaucoma—125–250 mg PO/IV bid to qid
Altitude sickness—250–500 mg PO bid beginning 48 h before ascent
Epilepsy—375–1000 mg (8–30 mg/kg/d) PO qd if sole agent; begin 250 mg qd if with other agents
Congestive heart failure—250–375 mg PO/IV qd (for best results, take on alternate days)
Drug-induced edema—250–375 mg PO/IV qd (for best results, take on alternate days)
Urinary alkalinization—5 mg/kg PO/IV bid or tid to maintain alkaline urine pH

- **Contraindications**—hypersensitivity to drug or class, hyponatremia, hypokalemia, depressed respiratory function, cirrhosis, hyperchloride acidosis, adrenocortical insufficiency
- **Caution**—hepatic and/or renal dysfunction

(*Continued*)

Acetazolamide — cont'd

Maternal Considerations

There are no adequate reports or well-controlled studies of **acetazolamide** in pregnant women. Pregnancy is not known to alter the impact, efficacy, and dosing of **acetazolamide**. ***Side effects*** include aplastic anemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatitis, paresthesias, loss of appetite, taste changes, dyspepsia, and polyuria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Acetazolamide** apparently crosses the human placenta. There is no suggestion of teratogenicity in humans despite a long clinical experience. One case report documents a preterm infant whose mother was treated for glaucoma throughout pregnancy with oral **acetazolamide**. When renal tubular acidosis developed, **acetazolamide** was detected in the child's serum, confirming transplacental passage. In another case report, the fetus was born with a sacrococcygeal teratoma. And in a third, the exposed infant demonstrated metabolic complications including metabolic acidosis, hyperbilirubinemia, hypocalcemia, and hypomagnesemia. In some rodents, **acetazolamide** is teratogenic (skeletal abnormalities consisting variably of ossification defects or some form of postaxial forelimb ectrodactyly in rats, urinary malformations in mice when combined with **amiloride**). The prevalence of defects is enhanced when combined with **ibuprofen**.

Breastfeeding Safety

Acetazolamide is not concentrated in the milk, and the neonatal exposure is <0.5% of the maternal dose. It is generally considered compatible with breastfeeding.

Drug Interactions

Acetazolamide may modify **phenytoin** metabolism and increase the serum level of **phenytoin**. By decreasing the GI absorption of **primidone,** it may decrease serum concentrations of **primidone**.
Acetazolamide reduces urinary excretion of **quinidine** and may enhance its effect.
It increases **lithium** excretion.
Acetazolamide may elevate **cyclosporine** levels.
Acetazolamide may reduce urinary excretion of amphetamine and may enhance its effect.
Additive effects of concomitant carbonic anhydrase inhibitor use.
Acetazolamide may potentiate the effects of folic acid antagonists.
Concomitant use of aspirin may lead to toxicity by enhancing tissue penetration.
Acetazolamide may potentiate effects of oral anticoagulants.

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Summary

Pregnancy Category: C
Lactation Category: S

- **Acetazolamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Acetylcysteine — (Acetyst; Alveolux; Bromuc; Mucomyst; Mucosil; Mucosol; Mukosil; Respaire)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class

Antidotes; Antioxidants; Mucolytics

Indications

Treatment of **acetaminophen** or *Amanita phalloides* toxicity; mucolytic in patients with cystic fibrosis

Mechanism

A glutathione precursor that breaks disulfide bonds caused by oxidation

Dosage With Qualifiers

Acetaminophen toxicity—begin 140 mg/kg PO by NG tube; thereafter, 70 mg/kg PO q4h ×15–20 doses
Mucolytic—1 nebulizer ampule q6–8 h; alternatively 2–5 mL of 10% solution or 600 mg in 3 divided doses

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—severe respiratory failure, asthma

Maternal Considerations

***N*-acetylcysteine** is a prototype antioxidant presently used nearly exclusively during pregnancy for the treatment of maternal drug toxicity associated with free radical excess such as that occurring with **acetaminophen**. There are no adequate reports or well-controlled studies of ***N*-acetylcysteine** in pregnant women. It has been used for the treatment of **acetaminophen** toxicity during pregnancy. ***N*-acetylcysteine** or another like compound may have a role in the treatment of several disorders associated with excess free radical generation, including preterm labor and preeclampsia. For example, its administration reduced maternal hypertension after uterine artery ligation in rats.
Side effects include bronchospasm, anaphylaxis, N/V, stomatitis, rhinorrhea, urticaria, and rash.

Fetal Considerations

***N*-acetylcysteine** rapidly crosses the human placenta, reaching equilibrium with maternal sera. In one trial, laboring women with chorioamnionitis were given 100 mg/kg of NAC every 6 h until delivery as part of an effort to protect the fetal brain. NAC was associated with benefit, and there were no untoward events. In laboratory studies, it reduces embryo toxicity associated with hyperglycemia, hypoxia, and sepsis. In other studies, it reduces the adverse fetal effects of maternal inflammation by in part blocking the inflammation-stimulated release of cytokines. Further, ***N*-acetylcysteine** prevents neuronal loss in chronically hypoxic mouse and guinea pig fetuses.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether ***N*-acetylcysteine** enters human breast milk. It is unlikely short-term administration for an acute problem would pose a risk to the nursing infant.

Drug Interactions

***N*-acetylcysteine** should not be mixed in solution with **tetracycline, oxytetracycline,** and **erythromycin lactobionate**.
Intestinal absorbants such as charcoal may reduce the absorption of ***N*-acetylcysteine.**

References

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Summary

Pregnancy Category: B
Lactation Category: S (likely)

- ***N*-acetylcysteine** is indicated for the treatment of either cystic fibrosis or **acetaminophen** overdose during pregnancy.
- Future investigation may demonstrate a role for ***N*-acetylcysteine** in the treatment of the fetus for a myriad of pathologic conditions that share excess free radical generation.

Acyclovir — (Acivir Cream; Acivir Eye; Avirax; Avorax; Clovicin; Clovix; Entir; Supra-Vir; Zovirax)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class
Antivirals

Indications
Primary or secondary herpes infection/suppression; treatment or prevention of *Varicella* pneumonia

Mechanism
A synthetic, acyclic purine nucleoside that inhibits DNA polymerase by direct incorporation

Dosage With Qualifiers
Genital herpes, recurrent—200 mg PO 5×/d ×10 d
Genital herpes, suppressive—400 mg PO bid for up to a year, or during pregnancy, from 36 w onward; with HIV, 400–800 mg PO 2–3×/d, or IV 5–10 mg/kg q8h ×5–10 d
Herpes zoster—800 mg PO 5×/d ×7–10 d
Ocular herpes—3% ointment 5×/d ×7–10 d
Varicella, acute—800 mg PO qid ×5 d
- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction or concurrent nephrotoxic drug

Maternal Considerations
Some 22% of pregnant women have genital HSV infection, and most of them are unaware. There is a long clinical experience free of obvious adverse effects. Treatment is not curative, but rather intended to reduce the duration of symptoms and viral shedding. Meta-analysis indicates prophylactic **acyclovir** beginning at 36 w reduces the risks for a clinical recurrence of genital herpes at delivery, cesarean section for recurrence, and herpes shedding at delivery. Suppression therapy is clinically effective and cost effective whether or not the primary infection occurred during the current pregnancy. Though it has not been specifically studied, the t/2 of **acyclovir** may be reduced during pregnancy, as it is excreted by the kidneys. Its combination with **zidovudine** alters the clearance of both agents in pregnant rats.
Side effects include seizures, coma, leukopenia, thrombocytopenia, renal dysfunction, N/V, diarrhea, headache, dizziness, lethargy, rash, and confusion.

Fetal Considerations
There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **acyclovir** crosses the human placenta. It is unclear whether maternal prophylaxis actually reduces the incidence of neonatal herpes. Postmarketing surveillance by Glaxo-Wellcome has not revealed any increase in or pattern of malformations after **acyclovir** exposure during the first trimester (756 pregnancies). A population-based study from Denmark that included 90 systemic and 995 topical exposures was likewise reassuring. Avoidance is preferred, as the death rate from neonatal herpes may exceed 25% despite high-dose **acyclovir** therapy. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety
Acyclovir is passively secreted and achieves concentrations in breast milk higher than maternal serum, and it is used to treat neonatal herpetic infection. It is generally considered compatible with breastfeeding. It has been estimated that the unsupplemented newborn would ingest 1–3 mg/d.

Drug Interactions
Probenecid and **cimetidine** increases the mean **acyclovir** t/2 and AUC. Urinary excretion and renal clearance are correspondingly lower.

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Summary	**Pregnancy Category: B** **Lactation Category: S** • **Acyclovir** significantly reduces the duration of shedding and the number of recurrent HSV outbreaks during pregnancy. • Prophylaxis to prevent recurrence should be initiated at 36 weeks.

Adalimumab — (Humira)

International Brand Names
None identified.

Drug Class	Immunosuppressant; antirheumatic
Indications	Arthritis, plaque psoriasis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis
Mechanism	Binds to tumor necrosis factor alpha (TNF-alpha) to interfere with the inflammatory processes
Dosage With Qualifiers	Crohn's disease and ulcerative colitis—160 mg SC × 1 on day1, then 80 mg SC × 1 on day 15, then 40 mg SC q2w on day 29. Rheumatoid arthritis—begin 1 mg/kg PO qd; increase 0.5 mg/kg/d after 6–8 w; max 2.5 mg/kg/d; alternatively, 40mg SC q2wk • **Contraindications**—hypersensitivity to drug or class, chronic or localized infections • **Caution**—tuberculosis, infection, sepsis, neurologic events, malignancies
Maternal Considerations	There are no adequate reports or well-controlled studies of **adalimumab** in pregnant women. Reports from more than 2000 pregnancies exposed to TNF-α inhibitors during the first trimester reveal minimal risks of spontaneous abortion, low birth weight, prematurity, or congenital malformations. According to the Adalimumab Pregnancy Registry, serious infections and tuberculosis occurred at a rate of 4.7 and 0.3 events/100 patient-years, respectively. No significant laboratory abnormalities were reported with **adalimumab**-plus-**methotrexate** compared with placebo-plus-**methotrexate**. Influenza-related AEs occurred in 5% of vaccinated patients compared with 14% of patients not vaccinated during the study. ***Side effects*** include headache, hypertension, nausea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. In one series, 24/38 (71%) pregnancies were exposed to anti-TNFα at conception/first trimester, 11/38 (29%) prior to conception, and 3 (11%) after paternal exposure. According to the Adalimumab Pregnancy Registry, relative risk of major birth defects and spontaneous abortions in adalimumab-exposed women was similar to that of unexposed women with RA and healthy women. There were no differences in outcomes among the groups. **Adalimumab** crosses the placenta and is detected in cord blood at birth at concentrations higher than in maternal serum and remains detectable for up to 6 months after birth. Neonatal exposure is expected to be highest in the third trimester. Animal studies are reassuring, revealing no evidence of teratogenicity or IUGR. In one prospective multicenter study, offspring of mothers who received combination therapy with **adalimumab** plus AZA/6-MP had a 35% increase in risk of infection at 9–12 months of age compared to those receiving monotherapy.
Breastfeeding Safety	There is no published experience in nursing women. Low concentrations of **adalimumab** are detected in breast milk.
Drug Interactions	No drug-drug interactions have been reported.
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Summary	**Pregnancy Category: B** **Lactation Category: U**

Adapalene — (Differin; Differine)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Dermatologics; Retinoids
Indications	Acne vulgaris
Mechanism	Binds retinoid nuclear receptors to interfere with cellular differentiation, keratinization, and inflammatory processes
Dosage With Qualifiers	Acne vulgaris—apply (0.1%) cream or gel to the affected area once daily at night • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	Systemic absorption of **adapalene** across human skin is low, with none being detected in the plasma of six patients treated for acne in a standardized fashion for 5 d with 2 g. There are no adequate reports or well-controlled studies of **adapalene** in pregnant women. Women of childbearing age should be fully informed of the risks and the importance of effective contraception. This also applies to patients with moderate forms of psoriasis, for which topical **tazarotene** is indicated. ***Side effects*** include erythema, dryness, burning, scaling, and photosensitivity.
Fetal Considerations	There are no adequate studies of **adapalene** in human pregnancy. It is unknown whether **adapalene** crosses the human placenta. Though the pharmacology is encouraging, there are several reports in humans associating **adapalene** with fetal malformation after cutaneous exposure. A meta-analysis, including 654 pregnant women exposed to topical retinoids and 1375 unexposed control pregnant women, revealed no major increase in the rates of major congenital malformation, spontaneous abortions, low birth weight, and prematurity. The available information is insufficient to conclude cause and effect. Oral administration to rodents at 100–200 × the MRHD increased the risk of malformation. No abnormalities were seen in pregnancies exposed to lower concentrations.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **adapalene** enters human breast milk. Considering the dose and route, it is unlikely to pose a significant risk to the breastfeeding neonate.
Drug Interactions	As **adapalene** may cause local irritation, simultaneous use of other topical agents such as medicated or abrasive soaps and cleansers, soaps and cosmetics with a strong drying effect, and products with high concentrations of alcohol should be avoided if possible. Caution is also recommended in using preparations containing sulfur, resorcinol, or salicylic acid in combination with **adapalene**. Other cutaneous antiacne treatments may be used in the morning when adapalene topical is used at night.
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Summary	**Pregnancy Category: C** **Lactation Category: U** • It is best to avoid topical retinoids in early pregnancy, as the disease process is rarely life threatening. • Women of childbearing age should be fully informed of the risks and the importance of effective contraception. • There are alternative agents for which there is more experience during pregnancy and lactation.

Adenosine — (Adenic; Adenocar; Adenocard; Adeno-Jec; Adenoscan; Adenosine Phosphate; ATP)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Antiarrhythmics; Diagnostics
Indications	Paroxysmal SVT
Mechanism	Interrupts reentry pathways by slowing AV node conduction
Dosage With Qualifiers	Paroxysmal SVT conversion—3–6 mg IV over 1–2 sec; may double to 6 mg and then 12 mg if no response after 1–2 min • **Contraindications**—hypersensitivity to drug or class, second- or third-degree heart block or sick sinus syndrome • **Caution**—asthma, chronic obstructive pulmonary disease
Maternal Considerations	An endogenous purine-based nucleoside, IV **adenosine** is the first choice for short-term management of paroxysmal supraventricular arrhythmia after a vagal maneuver fails. Co-administration of **midazolam** safely reduces recall of the unpleasant effects of **adenosine**. For long-term therapy, β-blocking agents with β_1 selectivity are first-line drugs; class Ic agents and the class III drug **sotalol** are also effective therapeutic alternatives. **Adenosine** has been used on multiple occasions during pregnancy to treat paroxysmal SVT. There are reports of preterm labor associated with adenosine administration. ***Side effects*** include arrhythmia (bradycardia, VF or ventricular tachycardia, asystole, complete heart block), bronchospasm, flushing, chest or groin pressure, dizziness, N/V, apprehension, palpitations, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Adenosine** crosses the human placenta and enhances placental perfusion. Rodent studies reveal no evidence of teratogenicity. **Adenosine** can be administered directly into the umbilical vein to achieve control of a fetal SVT. Although adenosine has a very short elimination t/2 (<10 s), transient fetal bradycardia has been observed during treatment of a maternal SVT with intravenous adenosine.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Adenosine** is a normal constituent of human breast milk, though the short t/2 suggests little, if any, of the exogenously administered **adenosine** will enter the milk.
Drug Interactions	**Adenosine** may be rarely associated with VF when combined with **digoxin** and **verapamil** use. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, **adenosine** should be used with caution in the presence of these agents. The effects of **adenosine** are antagonized by methylxanthines such as **caffeine** and **theophylline**. **Adenosine** effects are enhanced by **dipyridamole. Carbamazepine** may increase the degree of heart block produced by other agents.
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Summary	**Pregnancy Category: C** **Lactation Category: U** • Useful for the short-term treatment of either maternal or fetal tachycardia.

Albuterol — (Airet; Albuterol Sulfate; Asmalin; Asmanil; Asmavent; Butamol; Buventol; Proventil; Salbusian; Salbutamol; Theosal; Ventolin; Ventolin Rotacaps; Volmax)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Adrenergic agonists; Bronchodilators
Indications	Bronchospasm; exercise-induced asthma
Mechanism	A selective β_2-agonist
Dosage With Qualifiers	Bronchospasm—1–2 puffs MDI q4–6 h, max 12 puffs/d; or 2–4 mg PO tid or qid Exercise-induced asthma—2 puffs MDI ×1 given 15–30 min before exercise *NOTE: Numerous drug interactions are known. The reader should consult a detailed reference if the patient is or has recently been on a MAOI or TCA, a β-adrenoceptor antagonist, a diuretic, or **digoxin**.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hyperthyroidism, CV disease, diabetes mellitus, seizure disorder
Maternal Considerations	**Albuterol** has been used as a tocolytic in some countries given IV, SC, or PO (also see **terbutaline** or **ritodrine,** whose efficacy it compares to). There is no quality evidence it can halt preterm or term labor. β-Mimetic tocolysis is associated with pulmonary edema, especially with multiple gestation, or in women concurrently receiving glucocorticoid therapy to hasten fetal lung maturation, or in association with infection. The mechanism is unclear. Treatment consists of oxygen supplementation and diuresis. Maternal serum glucose and plasma insulin levels peak soon after cessation of therapy and return to preinfusion levels within 2–3 h. The decline in potassium is gradual and plateaus after 2 h. Once the **albuterol** infusion is stopped, the potassium returns to normal by 2 h. Total WBC counts increase within an hour of initiating therapy. There is no need to administer insulin for hyperglycemia and/or potassium for hypokalemia unless the patient is a known diabetic or is severely affected and requires immediate surgery. ***Side effects*** include bronchospasm with inhaler form, arrhythmia, tremor, nervousness, tachycardia, dizziness, headache, hypertension, nausea, hyperactivity, hypokalemia, and hyperglycemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Albuterol** appears to cross the human placenta, though the kinetics remain to be elucidated. Less than 10% is absorbed after inhalation. There is no convincing evidence of teratogenicity after first-trimester exposure. In general, long-term follow-up studies of infants exposed to β-mimetic tocolysis are reassuring. **Albuterol,** like other β-adrenoceptor agonists, is associated with a reduction in the incidence of RDS. Animal studies reveal ~10% of the circulating maternal albuterol reaches the fetus, but the amount in the fetal lungs is comparable to that in the maternal lungs. A single abstract suggests an increased risk of newborn retinopathy. **Albuterol** is teratogenic in mice at doses lower than those used in humans.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **albuterol** enters human breast milk. Other β-adrenoceptor agonists such as **ritodrine** and **terbutaline** are considered safe for breastfeeding. Systemic absorption after inhalation is 10% or less.
Drug Interactions	Use with other sympathomimetic agents may lead to deleterious CV effects. This does not preclude the judicious use of an adrenergic agonist aerosol bronchodilator. **Albuterol** should be administered with extreme caution to women using either MAOIs or TCAs (or within 2 w of discontinuation). β-Blockers may trigger severe bronchospasm in asthmatic women. However, under certain circumstances (e.g., as prophylaxis after MI), there may be no acceptable alternative to the use of a β-blocker in women with asthma. The ECG changes and/or hypokalemia secondary to non–potassium-sparing diuretics may be acutely worsened by β-agonists. Serum **digoxin** levels decrease about 20% after a single dose of either IV or oral **albuterol** to normal volunteers who ingested **digoxin** for 10 d.

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Summary

Pregnancy Category: C
Lactation Category: S

- **Albuterol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- As a tocolytic, **albuterol** has no advantage over any other β-adrenoceptor agonist, prolonging pregnancy on average 48 h over placebo.
- It is ineffective, as are all β-adrenoceptor agonists, when used for preterm labor prophylaxis.
- β-Adrenoceptor agonists should be avoided in diabetic women. If unavoidable, the patient should be aggressively covered with a short-acting insulin.

Alendronate — (Fosamax)

International Brand Names

Log on to ExpertConsult.com for a list of all international brand names.

Drug Class

Bisphosphonates; Calcium metabolism

Indications

Osteoporosis

Mechanism

Inhibits osteoclast resorption

Dosage With Qualifiers

Osteoporosis, postmenopausal treatment—10 mg PO qd, or 70 mg PO once a week taken with meals
Osteoporosis, postmenopausal prevention—5 mg PO qd, or 35 mg PO once per week taken with meals
Osteoporosis, steroid induced—5 mg PO qd taken with meals
NOTE: Avoid supine position.

- **Contraindications**—hypersensitivity to drug or class, hypocalcemia, severe renal dysfunction
- **Caution**—upper GI disease

Maternal Considerations

There are no adequate reports or well-controlled studies of **alendronate** in pregnant women. **Alendronate** is superior to **conjugated estrogens** (with or without **medroxyprogesterone**) for the prevention of bone loss in older adult women, though the combination is superior. Drug levels may persist in bone for long periods of time, leading to inadvertent pregnancy exposure. ***Side effects*** include esophagitis, gastritis, dysphagia, esophageal ulcer, N/V, abdominal pain, arthralgia, myalgias, back pain, constipation, diarrhea, headache, chest pain, flulike syndrome, and peripheral edema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Adverse effects of bisphosphonates on fetal outcomes have been seen in animal studies, but the doses used were much higher than those typically used in clinical practice. One review identified 15 reports of bisphosphonate use before and/or during pregnancy (in total, 65 mother-child pairs); the agents used included alendronate, ibandronate, and risedronate, among many, with the reported durations of use ranging from one-time treatments to months or years. Adverse outcomes observed included marginal decreases in gestational age and birth weight and transient neonatal electrolyte abnormalities (e.g., hypocalcemia, hypercalcemia, hyperphosphatemia); however, no long-term health consequences were reported in any infant. **Alendronate** crosses the rodent placenta, decreasing bone density and delaying delivery. Both the total and ionized calcium are reduced in the rodent mother and fetus. The toxic effects are reversed by calcium administration.

(*Continued*)

Alendronate — cont'd

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **alendronate** enters human breast milk. However, the risk to the breastfed neonate is likely low considering the low maternal systemic levels.

Drug Interactions

Combined use of HRT and **alendronate** in postmenopausal osteoporotic women revealed the suppression of bone turnover was greater with the combination.
Calcium supplements, antacids, and some oral medications interfere with absorption of **alendronate**. Women should wait at least ½ h after taking **alendronate** before taking any other oral medications.
The incidence of upper GI adverse events is increased in women receiving daily doses of **alendronate** greater than 10 mg and **aspirin**-containing products.
Food, beverages (other than water), and herbal products may interfere with the absorption of alendronate. Women should wait at least ½ h after taking **alendronate** before consuming.

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Summary

Pregnancy Category: C
Lactation Category: U

- **Alendronate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Alfentanil — (Alfenta; Alfentanyl; Rapifen)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class

Analgesics, narcotic

Indications

Analgesia either alone or in combination for labor or gynecologic pain

Mechanism

A short-acting lipophilic opioid

Dosage With Qualifiers

Anesthesia, induction—130–245 mcg/kg IV (primarily with underlying cardiac disease undergoing a prolonged surgical procedure); more commonly 8–50 mcg/kg at induction to blunt the pressor response to tracheal intubation
Anesthesia, maintenance—3–15 mcg/kg IV prn, or 0.5–1 mcg/kg/min continuous infusion
NOTE: Chest wall rigidity is common, and neuromuscular blockers are usually given to enable mask ventilation before tracheal intubation.
Conscious sedation—3–8 mcg/kg IV ×1

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—chest wall rigidity; N/V; bradycardia; hepatic, renal, or pulmonary dysfunction; head injury; bowel obstruction

Maternal Considerations

Alfentanil is a short-acting narcotic with rapid onset. As with other lipophilic opioids, **alfentanil** reduces the total dose of local anesthetic analgesic needed to provide comfort when combined with **bupivacaine** for epidural analgesia while diminishing the likelihood of an undesired motor blockade. IV **alfentanil** given just prior to intubation reduces the associated pressor response in both healthy and preeclamptic women.
Side effects include respiratory arrest or depression, arrhythmia, seizure, coma, abuse or dependency, muscle rigidity, N/V, dizziness, hypertension, hypotension, tachycardia, bradycardia, confusion, sweating, dry mouth, constipation, and urinary retention.

Fetal Considerations	**Alfentanil** crosses the placenta when given IV, though its transfer rate is lower than **fentanyl** (which approximates **antipyrine**). Neither human embryo toxicity nor teratogenicity is reported, though first-trimester human data are limited. **Alfentanil** is embryotoxic in rodents when given for 10–30 d at doses 2–3× the MRHD. One limited monkey study concluded offspring had impaired ability to do simple cognitive tasks at 2–3 mo of age after exposure at 14 w gestation. Lipophilic and hydrophilic characteristics of the drug influence placental transfer, as do fluctuations in maternal flow. Neonatal depression characterized by reduced active and passive tone is reported when **alfentanil** is given shortly before delivery. Occasionally, a narcotic antagonist is necessary. There are no reported fetal or neonatal effects after its use for conduction anesthesia.
Breastfeeding Safety	**Alfentanil** is excreted into human breast milk, though the amount excreted is too small to have any significant effect on the newborn.
Drug Interactions	The magnitude and duration of CNS and CV system effects may be enhanced when administered with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged. **Erythromycin** may inhibit **alfentanil** clearance and increase the risk of prolonged or delayed respiratory depression. **Cimetidine** reduces the **alfentanil** clearance. **Fluconazole** reduces the **alfentanil** clearance. **Diltiazem** reduces the **alfentanil** clearance. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma **alfentanil** clearance and prolong recovery.
References	Ashton WB, James MF, Janicki P, Uys PC. Br J Anaesth 1991; 67:741-7. Cooper RA, Devlin E, Boyd TH, Bali IM. Eur J Anaesthesiol 1993; 10:183-7. Giesecke AH, Rice LJ, Lipton JM. Anesthesiology 1985; 63:A284. Giroux M, Teixera MG, Dumas JC, et al. Biol Neonate 1997; 72:133-41. Golub MS, Eisele JH Jr, Donald JM. Am J Obstet Gynecol 1988; 159:1280-6. Rout CC, Rocke DA. Br J Anaesth 1990; 65:468-74. Scherer R, Holzgreve W. Eur J Obstet Gynecol Reprod Biol 1995; 59:S17-29. Zakowski MI, Ham AA, Grant GJ. Anesth Analg 1994; 79:1089-93.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Alfentanil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Allopurinol — (Aipico; Alloremed; Alloscan; Alonol; Aloral; Aluline; Aluprin; Apurol; Isanol; Lopurin; Lysuron; Unizuric; Uricemil; Uriconorm-E; Zyloprim; Zyroric)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Antigouts; Antioxidants; Purine analogs
Indications	Gout, nephrolithiasis secondary to urate or calcium oxalate stones
Mechanism	A xanthine oxidase inhibitor that interferes with the conversion of xanthine and hypoxanthine to uric acid
Dosage With Qualifiers	Gout prophylaxis—100–800 mg PO qd; titrate dose until uric acid <6 mg/dL Urate nephrolithiasis prophylaxis—100–800 mg PO qd Calcium oxalate calculi—200–300 mg PO qd *NOTE: Renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction

(*Continued*)

Allopurinol — cont'd

Maternal Considerations

Allopurinol is rarely indicated for traditional indications in pregnant or lactating women, and there are no adequate reports or well-controlled studies of **allopurinol** in pregnant women. There are several case reports. One woman treated for primary gout during pregnancy with **allopurinol** delivered a healthy child at 35 w. Another documents a woman treated for a gout flare associated with gestational diabetes, also without adverse events. A report documents 13 cases of **allopurinol** and thiopurine co-therapy used successfully to manage inflammatory bowl diseases during pregnancy without attributable adverse fetal effects. **Allopurinol** is also used during pregnancy for women undergoing treatment of acute leukemia. Of future interest is its potential as an antioxidant. **Allopurinol** was used unsuccessfully in one trial for the treatment of established preeclampsia.
Side effects include agranulocytosis, aplastic anemia, thrombocytopenia, hepatic dysfunction, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, rash, diarrhea, pruritus, nausea, and gout flare.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses.
Allopurinol readily crosses the ovine placenta, where it reaches equilibrium within 30 min. It reduces superoxide generation in the brains of fetuses subject to intermittent umbilical cord occlusion. One multicenter randomized placebo controlled trial concluded that maternal treatment with **allopurinol** during fetal hypoxia lowered neuronal damage markers in female but not male cord blood; developmental outcome was not reported. There is no evidence that **allopurinol** is teratogenic in humans. Cleft palate and skeletal defects are reported in some rodents. In 31 prospectively identified pregnancies with **allopurinol** exposure during at least the first trimester, an overall rate of major malformations (3.7%) and of spontaneous abortions (cumulative incidence 11%, 95% CI 3–40)—each within normal range—was reported.

Breastfeeding Safety

Allopurinol and its metabolite oxypurinol are excreted into breast milk to a limited degree and are considered compatible with breastfeeding. The average daily dose of **allopurinol** consumed by a 3-kg neonate would be 0.6 mg and that of oxypurinol would be 24 mg.

Drug Interactions

Allopurinol inhibits xanthine oxidase–catalyzed oxidation of **mercaptopurine** and **azathioprine** to 6-thiouric acid. Women taking **allopurinol** require a one-fourth to one-third reduction in their dose of **mercaptopurine/azathioprine**.
Allopurinol prolongs the t/2 of **dicumarol**. The PT should be reassessed periodically in women receiving both drugs.
Chlorpropamide's t/2 may be prolonged by **allopurinol,** as **allopurinol** and **chlorpropamide** compete for excretion by the renal tubule. The risk of hypoglycemia secondary to this mechanism may be increased in women with renal insufficiency.
Allopurinol may increase the t/2 of **vidarabine**.
Allopurinol may inhibit hepatic oxidation of phenytoin.
High doses of **allopurinol** (300 mg bid) inhibit the clearance of theophylline in normal subjects.
Co-administration of **allopurinol** may increase the plasma concentration of **cyclosporine**.

References

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Summary

Pregnancy Category: C
Lactation Category: S

- **Allopurinol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Almotriptan — (Axert)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Serotonin receptor agonists
Indications	Migraine headache, acute
Mechanism	Binds with high affinity to 5-HT_{1D}, 5-HT_{1B}, and 5-HT_{1F} receptors, causing cranial vessel constriction
Dosage With Qualifiers	Migraine headache, acute—6.25–12.5 mg PO ×1; may repeat ×1 q2h; max 25 mg/24 h *NOTE: Renal and hepatic dosing.* • **Contraindications**—hypersensitivity to drug or class, uncontrolled hypertension, ischemic heart disease, coronary spasm, basilar or hemiplegic migraines, 5-HT_1 agonist or ergot use <24 h • **Caution**—cerebrovascular disease, PVD, ischemic bowel, cardiac risk factors, hepatic or renal dysfunction
Maternal Considerations	Migraine is a paroxysmal disorder with attacks of headache, N/V, photo- and phonophobia, and malaise. There is no published experience with **almotriptan** during pregnancy. Similar agents such as **sumatriptan** are associated with an increased risk of preterm birth. It is likely the metabolism of **almotriptan** is decreased during pregnancy, thus increasing the risk of toxicity. ***Side effects*** include hypertensive crisis, MI, coronary spasm, ventricular arrhythmias, CVA, peripheral vascular ischemia, bowel ischemia, N/V, somnolence, headache, paresthesias, and chest or jaw or neck pain or pressure.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **almotriptan** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically, though embryo lethality was observed at 1000× the MRHD, and prolongation of pregnancy at 160× the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **almotriptan** enters human breast milk. **Almotriptan** is concentrated in rat milk (7× higher rat plasma).
Drug Interactions	SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) may rarely cause weakness, hyperreflexia, and incoordination when given with 5-HT_1 agonists. MAOIs (e.g., moclobemide) may decrease **almotriptan** clearance. Verapamil may increase **almotriptan** plasma concentrations. **Ketoconazole** and other potent CYP3A4 inhibitors increased the AUC for **almotriptan** by 60%. Although the interaction between **almotriptan** and other potent CYP3A4 inhibitors (e.g., **itraconazole, ritonavir, erythromycin**) has not been studied, increased levels to **almotriptan** are to be expected when used with these medications.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Almotriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Aloe Vera — (Aloe Vera; Cape; Zanzibar; Socotrine)

International Brand Names
None identified.

Drug Class	Dermatologics
Indications	Wound healing
Mechanism	May neutralize or bind to the fibroblast growth factor-2 receptor
Dosage With Qualifiers	Wound healing—applied topically using a variety of formulations • **Contraindications—**hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Aloe vera** gel is extracted from the inner layer of the leaf and contains a myriad of compounds. Two FDA advisory panels concluded there was insufficient evidence that **aloe vera** is useful for the treatment of minor burns, cuts, or vaginal irritation. However, one study suggested **aloe vera** may accelerate wound healing by promoting gap junctional intercellular communication and proliferation of human skin fibroblasts. There are no adequate reports or well-controlled studies in pregnant women. It should never be ingested. ***Side effects*** include severe gastric cramping and diarrhea if taken internally.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses.
Breastfeeding Safety	There is no published experience in pregnancy. However, considering the topical route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No drug-drug interaction studies in human subjects have been conducted.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Aloe vera** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Alosetron Hydrochloride — (Lotronex)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Antidiarrheals; Gastrointestinals; Serotonin receptor antagonist
Indications	Diarrhea-predominant irritable bowel syndrome
Mechanism	A selective and potent antagonist of the serotonin 5-HT_3 receptor
Dosage With Qualifiers	Diarrhea associated with irritable bowel syndrome—1 mg PO bid • **Contraindications**—hypersensitivity to drug or class, constipation • **Caution**—unknown
Maternal Considerations	There are no published reports of **alosetron** use during pregnancy. ***Side effects*** include ischemic colitis, constipation, hypertension, allergic rhinitis, dyspepsia, and depressive disorders.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **alosetron** crosses the human placenta. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically, with the exception of the mouse, where cleft palate and skeletal defects were reported.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **alosetron** enters human breast milk. **Alosetron** is excreted into the milk of lactating rats.
Drug Interactions	Co-administration of **alosetron** and **fluvoxamine** is contraindicated. **Alosetron** is metabolized by a variety of hepatic CYP drug-metabolizing enzymes. **Fluvoxamine** inhibits CYP1A2, CYP3A4, CYP2C9, and CYP2C19. **Fluvoxamine** increases mean **alosetron** plasma AUC some sixfold and prolongs the t/2 threefold. Other moderate CYP1A2 inhibitors, including quinolone antibiotics and **cimetidine**, should also be avoided unless necessary. **Ketoconazole** is a strong inhibitor of CYP3A4 and increases **alosetron** plasma AUC by close to one-third. Other strong CYP3A4 inhibitors, such as **clarithromycin, telithromycin,** protease inhibitors, **voriconazole,** and **itraconazole,** have not been evaluated but should be used with caution with **alosetron**. Based on several *in vitro* and *in vivo* studies, it is unlikely **alosetron** will inhibit the hepatic metabolic clearance of drugs metabolized by the major CYP enzyme 3A4, as well as the CYP enzymes 2D6, 2C9, 2C19, 2E1, or 1A2.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Alosetron** is rarely indicated during pregnancy and should be used only when the benefits outweigh any theoretic risks.

Alprazolam — (Alpralid; Alprazolam Intensol; Altraxic; Apo-Alpraz; Xanax; Xanax TS; Xanolam; Zoldac; Zolam; Zopax)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Anxiolytics; Benzodiazepines; Sedatives
Indications	Acute anxiety
Mechanism	A short-acting benzodiazepine that reduces anxiety by enhancing GABA effects
Dosage With Qualifiers	Antianxietal—0.25–0.5 mg PO tid, max 4 mg/d Panic disorder—0.5 mg PO tid, up to 1 mg after 3–4 d • **Contraindications**—hypersensitivity to drug or class, glaucoma, pregnancy, CNS depression • **Caution**—hepatic or renal dysfunction
Maternal Considerations	The number of pregnant women using **alprazolam** seems to be growing, yet there remain few published reports of its use during pregnancy. Abrupt cessation of therapy is associated with a discontinuation-emergent syndrome that includes neuropsychiatric, GI, dermatologic, CV, and visual symptoms. ***Side effects*** include physical dependence, syncope, tachycardia, seizures, respiratory depression, coma, drowsiness, light-headedness, dry mouth, depression, headache, constipation, diarrhea, N/V, insomnia, blurred vision, hypotension, increased salivation, and dermatitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Although there is no evidence that **alprazolam** is a human teratogen by either case reports or postmarketing surveillance, **diazepam** has been associated with fetal malformations. There is also concern based on studies with other benzodiazepines that postnatal behavior might be altered by antenatal exposure. Neonatal withdrawal has been reported. Treatment with **phenobarbital** is beneficial. Mice exposed to **alprazolam** demonstrate more individual than group activities and avoid open areas, and the males are more aggressive.

(*Continued*)

Alprazolam — cont'd

Breastfeeding Safety

Alprazolam enters breast milk by passive diffusion, achieving an M:P ratio of 0.36. This is approximately 3% of the weight-adjusted maternal dose. Though the risk is reasonably small, **alprazolam** should be avoided during lactation because of the potential that it might alter neurodevelopment and because of the documented risks of withdrawal.

Drug Interactions

Benzodiazepines such as **alprazolam** can produce additive CNS depressant effects when given with other psychotropic medications, anticonvulsants, antihistaminics, ethanol, and other drugs that themselves produce CNS depression.
Drugs or diseases that cause dry mouth or raise stomach pH may slow disintegration or dissolution, resulting in slowed or decreased absorption.
Alprazolam metabolism requires CYP3A hydroxylation. Drugs that inhibit this pathway can profoundly affect the clearance of **alprazolam**. Known drugs of concern include **fluoxetine, propoxyphene,** and oral contraceptives.
Clinical studies of other benzodiazepines suggest a possible drug interaction between **alprazolam** and **diltiazem, isoniazid,** macrolide antibiotics such as **erythromycin** and **clarithromycin,** and grapefruit juice. *In vitro* studies of other benzodiazepines suggest possible interactions with **ergotamine, cyclosporine, amiodarone, nicardipine,** and **nifedipine**.
Carbamazepine can increase **alprazolam** metabolism and thus decrease plasma levels.
Co-administration of **nefazodone** or **fluvoxamine** with **alprazolam** increases the peak concentrations, AUC, and t/2 of **alprazolam.**
Cimetidine impairs clearance of **alprazolam** and increases t/2.
HIV protease inhibitors (e.g., **ritonavir**) may impair **alprazolam** clearance, prolong t/2, and enhance clinical effects.

References

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Summary

Pregnancy Category: D
Lactation Category: NS (likely)
- **Alprazolam** should be avoided during pregnancy and lactation unless there are no safer options.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Alteplase — (Actilyse; Activacin; Activase; TPA)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class

Thrombolytics

Indications

Acute MI, pulmonary embolus, acute ischemic stroke

Mechanism

Human recombinant tissue plasminogen activator is a serine protease that converts plasminogen to plasmin in the presence of fibrin.

Dosage With Qualifiers

Acute MI—within 4 h of symptom onset and based on weight: <67 kg, 15 mg bolus IV, followed by 0.75 mg/kg IV over the next 30 min (not to exceed 50 mg), then 0.5 mg/kg over the next 60 min (not to exceed 35 mg); >66 kg, 15 mg bolus IV, followed by 50 mg IV over 30 min, then 35 mg over the next 60 min
Pulmonary embolus—100 mg IV over 120 min; initiate **heparin** therapy near the end or immediately following the **alteplase** when either the PTT or TT returns to <2× normal
Acute ischemic stroke—given within 4 h of symptom onset: 0.9 mg/kg IV over 60 min; begin with 10% of dose as an IV bolus over 1 min (max total dose 90 mg)
- **Contraindications**—hypersensitivity to drug or class, intracranial hemorrhage, seizure at onset of stroke, internal bleeding, intracranial neoplasm, aneurysm, hypertension (>185/110 mmHg S/D)
- **Caution**—unknown

Maternal Considerations	There are no adequate reports or well-controlled studies of **alteplase** in pregnant women. There are case reports of its use during pregnancy for the treatment of PE, MI, and peripheral thrombosis without an apparent increase in risk for hemorrhage, abruption, and PROM or preterm labor. ***Side effects*** include cerebral hemorrhage, arrhythmias, severe bleeding, anaphylaxis, hypotension, N/V, and fever.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **alteplase** crosses the human placenta. It could theoretically interfere with implantation. In light of its high molecular weight, **alteplase** is unlikely to cross the placenta. No maternal or fetal toxicity was evident at 0.65 times (1 mg/kg) the human dose in pregnant rats and rabbits dosed during organogenesis. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. Although tissue plasminogen activator is a normal constituent of human breast milk, it is unknown whether **alteplase** increases that level.
Drug Interactions	Drugs that alter platelet function (e.g., **aspirin, dipyridamole, abciximab**), in addition to **heparin** and vitamin K antagonists, may increase the risk of bleeding if administered prior to, during, or after **alteplase**. There are postmarketing reports of orolingual angioedema associated with **alteplase**.
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Summary	**Pregnancy Category: C** **Lactation Category: U** • **Alteplase** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • It is effective for acute thrombotic events that place the patient's survival in question.

Amantadine — (Contenton; Endantadine; Infectoflu; Mantandan; Shikitan; Symmetrel; Topharmin)

International Brand Names
Log on to ExpertConsult.com for a list of all international brand names.

Drug Class	Antivirals; Dopaminergics; Extrapyramidal disorders
Indications	Treatment or prevention of influenza A, treatment of extrapyramidal reactions or parkinsonism
Mechanism	Unknown; appears to interfere with release of viral nucleic material into the host cell
Dosage With Qualifiers	Influenza A treatment—200 mg PO qd until 24–48 h after symptoms resolve Influenza A prophylaxis—200 mg PO qd beginning immediately after exposure and continuing at least 10 d Extrapyramidal reactions—100 mg PO qd to tid (max 300 mg/d) Parkinsonism—begin 100 mg PO qd, increase to bid after 1 w, max 400 mg/d; reduce to 100 mg/d if taking other antiparkinsonism drugs *NOTE: Renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—seizure disorder, heart failure, liver disease, CV disease, geriatric population

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