Cardiovascular Pharmacotherapeutic Considerations During Pregnancy and Lactation

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Abstract: Cardiovascular drugs are often used in pregnancy for the treatment of maternal and fetal conditions. Mothers could also require continued postpartum drug therapy. Most cardiovascular drugs taken by pregnant women can cross the placenta and therefore expose the developing embryo and fetus to their pharmacologic and teratogenic effects. These effects are influenced by the intrinsic pharmacokinetic properties of a given drug as well as by the complex physiological changes occurring during pregnancy. Many drugs are also transferred into human milk and therefore can potentially have adverse effects on the nursing infant. This 2-part article summarizes some of the available literature concerning the risks and benefits of using various cardiovascular drugs and drug classes during pregnancy and lactation. Included in the discussion are cardiac glycosides, antiarrhythmic drugs, drugs used to treat both acute and chronic hypertension, cholesterol-lowering agents, anticoagulants, thrombolytics, and antiplatelet drugs.

Key Words: pregnancy, lactation, antiarrhythmics, antihypertensives, cardiovascular drugs, antihyperlipidemics, anticoagulants

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CLINICAL PHARMACOLOGY

During pregnancy, certain physiological changes occur in the cardiovascular, renal, gastrointestinal, and endocrine systems that could influence the pharmacokinetics of drugs (Table 1),[1] thereby affecting drug transfer across the maternofetal unit.

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Decreased motility in the gastrointestinal tract can influence drug absorption. Drug stagnation can occur as a result of reduced gastric motility.[2] Increased gastric pH resulting from decreased acid secretion and increased production of alkaline mucus can affect the degree of ionization and solubility of drugs.[3] Longer transit time through the gastrointestinal tract could allow for increased metabolism of drugs in the gut wall or, conversely, more complete drug absorption leading to increased bioavailability.[4,5]

During pregnancy, increases in maternal intravascular and extravascular fluid volumes by 5 to 8 L also could affect drug distribution.[6,7] Because of the greater physiological volume, higher loading doses could be required to produce expected serum drug concentrations. However, steady-state concentrations resulting from chronic drug administration do not differ from the nonpregnant state.[4] The plasma volume is increased progressively by 50% and is associated with a progressive fall in the plasma protein concentration.[6–8] Serum albumin, the principal drug-binding protein, decreases progressively throughout pregnancy.[4] Together with the altered binding of α_1-acid glycoprotein,[9,10] the increase in fatty acids and lipids and hormonal changes leads to an increase of the unbound drug fraction.[4] This could partially explain the increased clearance seen with some drugs and the resultant decrease in total drug concentration. Tissue-to-plasma distribution of drugs also is increased.[11] Because the bound drug concentration is decreased, the average total drug concentration at steady state will be less, although the mean steady-state serum concentration of the unbound drug, which is therapeutically active, remains unchanged. Therefore, the serum concentration of total drug in pregnant women will underestimate the concentration of free drug and could lead to unnecessary increases in drug dosage.[12] Although the mean steady-state concentration does not change, a greater fluctuation in the unbound drug concentration will occur within a dosing interval, potentiating toxic effects at the beginning of a dosing interval or loss of therapeutic effect at the end of an interval. Consequently, more frequent dosing without a change in daily dosage could be required.[12]

TABLE 1. Factors Affecting Drug Kinetics During Pregnancy

Process	Mother	Placental–Fetal Unit
Absorption	Increased plasma progesterone level reduces intestinal motility resulting in a 30–50% increase in gastric and intestinal-emptying time	Only free (unbound) drug can cross the placental barrier
	Gastric acid and mucus secretions are reduced resulting in increased gastric pH	Nonionized, highly lipid-soluble molecules penetrate biologic membranes more quickly than less lipid-soluble ionized molecule
		Maternal and fetal pH are important determinants of placental transfer, especially for weakly acidic or basic drugs (weakly basic drugs cross the placenta easily in the nonionized form but will ionize in the relatively acidic fetal blood, resulting in more drug transfer to the fetus (this is referred to as "ion trapping")
	Increased cardiac output and tidal flow increase pulmonary absorption of drugs	
Distribution	A 50% plasma volume expansion can result in altered volume of distribution of some drugs	Half the fetal circulation (umbilical vein) directly reaches the heart and brain, bypassing the liver
	Mean total body water increases by 8l, of which 40% is to maternal tissue (remainder to placenta, fetus, and amniotic fluid)	
Protein binding	Reduced number of available binding sites because of occupancy by steroid and placental hormones	Drug affinity for fetal plasma proteins can be less (eg ampicillin) or greater (eg salicylates) than affinity for maternal proteins
	Dilutional hypoalbuminemia occurs, decreasing protein binding	
Elimination	Changes in levels of endogenous substance can result in increases or decreases in hepatic elimination of drugs (eg phenytoin metabolism is increased, possibly as a result of the stimulation of microsomal enzymes by progesterone; the ophylline metabolism is decreased, possibly	Elimination of drugs from the fetus is primarily by diffusion of the drug back to the maternal compartment (although there is some evidence that both the placenta and fetus are capable of metabolizing drugs)
	as a result of competitive inhibition by progesterone and estradiol)	As the fetal kidney matures, more drugs are excreted into the amniotic fluid
	A 25–50% increase in renal plasma flow and a 50% increase in glomerular filtration rate can increase renal elimination of drugs*	

*The changes in renal drug elimination are usually clinically insufficient to require dosage alteration.

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The metabolism of many drugs is altered during pregnancy. The principal change in cardiovascular hemodynamics is an increase of 30% to 50% in cardiac output.[6,8,13] Consequently, renal blood flow and glomerular filtration rate rise rapidly, increasing by 50% by the fourth month of gestation.[14] Therefore, certain drugs and their metabolites that principally are excreted by the kidneys will be cleared more rapidly during pregnancy, resulting in subtherapeutic concentrations with the usual nonpregnant dosage regimen. The liver is another major organ of drug metabolism. Hepatic clearance depends on hepatic blood flow, the binding affinity of drugs, and the metabolizing enzyme system.[4] Progesterone increases maternal hepatic enzymatic activity, resulting in increased drug clearance. The cytochrome P450 system could also be activated in pregnancy, leading to increased drug clearance.[15] Also, some drug biotransformation could occur in the placenta and the fetal liver.[16] The placenta contains several enzymatic systems that transform certain drugs into toxic and nontoxic metabolites.[4] The fetus also could participate in drug metabolism after the eighth week of gestation.[26]

Drug transfer across the placenta can occur by simple diffusion for almost all drugs when taken in significant amounts by the mother.[4] The rate of diffusion obeys Fick's Law, which states that the diffusion rate is directly proportional to the maternal–fetal concentration gradient and the surface area of the placenta and is inversely proportional to the thickness of the placental membrane. Drug properties such as degree of lipid solubility, molecular weight, degree of

ionization, and the pH difference between maternal and fetal fluids also could influence the rate of passage. Therefore, diffusion is facilitated by a drug's high degree of lipid solubility, low degree of ionization, and low molecular weight. The transfer of weak acids and bases further depends on their pKA and the pH of the maternal and fetal fluids. Fetal plasma tends to be slightly more acidic than maternal plasma. Weak bases will become ionized after crossing the placental membrane and therefore become "trapped" in the more acidic fetal circulation. Indeed, in fetal acidosis, such "drug trapping" could lead to higher drug concentrations in the fetus than the mother.

In the 2 weeks after conception, the embryo is relatively resistant to exogenous toxicity. Abortion generally results from any damage during this time.[4] Congenital malformations generally are caused by drug toxicity during the first trimester and depend on the nature of the drug, the duration of fetal exposure, the genetic susceptibility of the fetus, and its accessibility to the fetus.[4] Consequently, drug administration in the first trimester should be avoided as much as possible. In the second and third trimesters, interference with fetal growth and development is the major potential hazard of drug exposure.[17] Delayed teratogenic effects could occur long after initial maternal drug ingestion.[18] Therefore, long-term evaluation of any pharmacologic agent given during pregnancy is necessary before its safety can be accepted, and assessment of the benefit of drug therapy in a pregnant patient in light of its known and unknown potential risks to the fetus must be considered.

Furthermore, the issue of a mother who requires continuing drug therapy but wants to breastfeed her child poses potential problems. Many drugs taken by the mother will eventually appear in human milk.[19] The drug level in milk depends on the physiochemical properties of the drug, the degree of plasma protein binding, and the maternal serum concentration.[20] Therefore, unionized drugs with minimal protein binding and high lipid solubility are found more readily in breast milk. Fortunately, because the amount of drug excreted in milk is rarely more than 1% to 2% of the dose administered to the mother, only a small number of drugs are considered prohibited to the nursing mother.[4] Like with transplacental drug transfer, the lower pH in breast milk compared with plasma acts as an "ion trap" for weak bases. Those compounds can accumulate in relatively high concentrations in milk compared with plasma. Conversely, acidic compounds tend to be inhibited from entering breast milk.[20] The milk/plasma ratio is often used as a measure of drug transfer into milk. However, the absence of a standard definition limits the usefulness of this value in clinical practice. These values are often calculated based on milk and plasma concentrations at different time points along a dosing interval. Many investigators also report the ratio of areas under the milk and plasma concentration curves.[19,20] Consequently, the best method for predicting potential drug effects on the nursing infant is by estimating the total amount of drug ingested in the breast milk.[21]

In this article, cardiac glycosides and various antiarrhythmic agents are discussed with regard to pregnancy and lactation. In the second of this 2-part article, we will discuss antihypertensives, antihyperlipidemics, and anticoagulants.

CARDIAC GLYCOSIDES

Numerous animal and human studies have shown that both digoxin and digitoxin are transferred readily across the placenta. Okita and colleagues[22] observed low levels of transplacental digitoxin present in the fetus after 3 to 5 hours of an intravenous injection of digitoxin to the mother. Increasing transplacental passage of digoxin is observed as pregnancy progresses, presumably as the maternofetal placental unit becomes more developed. Saarikoski[23] injected a single dose of radioactive digoxin into pregnant women before legal abortion and observed low levels in fetal tissues. He concluded that in the first half of gestation, digoxin uptake by the fetus is limited. Rogers and colleagues[24] found similar serum concentrations of digoxin in the newborn at term and the mother 6 hours after the last oral dose received by the mother.

No teratogenicity has been associated with the use of the cardiac glycosides. However, adverse effects on the fetus have been found in mothers who developed digitalis toxicity. Sherman and Locke[25] reported a case of maternal digitalis toxicity associated with electrocardiographic changes in the newborn and subsequent death of the infant. Potondi reported another case in which digitalis overdosing of the pregnant mother led to an eventual miscarriage.[26]

Occasionally, mothers on chronic treatment with digitalis have been observed to give birth to infants with low birth weights. Whitsett and Wallick[27] postulated that digitalis could alter the maternal–placental transfer of amino acids to the fetus. Weaver and Pearson[28] examined 22 digitalis-treated women with cardiac disease and found that the mean gestational period and the mean duration of labor, compared with 64 women not on digitalis, were both shorter in length. The investigators concluded that these findings were probably related to the direct effects of chronic digitalis therapy on the myometrium. Moreover, in observing similar results in the percentile weights related to the gestational age of the infants in both groups, they further concluded that the lower birth weight of infants on digitalis was probably the result of relative prematurity rather than growth retardation.

Digoxin has become a mainstay in the treatment of fetal arrhythmias, providing a 80% success rate in cardioverting supraventricular tachycardias.[29,30] Its cardiotonic effects also play a role in the treatment of fetal cardiac failure/hydrops fetalis in the absence of tachyarrhythmias. Digoxin is considered by some as the routine drug of choice in treating fetal

arrhythmias.[31] However, studies have shown that the success of digoxin is diminished in cases involving fetal hydrops.[29] This could be the result of the reduced transplacental passage of digoxin and lower fetal/cord blood levels. Therefore, higher doses are required in these cases coupled with close maternal toxicity monitoring. It is recommended that earlier intervention be used in the treatment of fetal arrhythmias complicated by hydrops or cardiac failure with the addition of secondary agents and/or direct fetal administration.[29] The efficacy of digoxin alone is also diminished in the treatment of fetal atrial flutter when compared with the success seen in supraventricular tachycardia.[32] This is particularly noteworthy in fetuses with heart failure. In addition, like with adults, Wolff-Parkinson-White syndrome could worsen with in utero digoxin exposure.[33] Finally, intravenous digoxin treatment causes a more rapid cardioversion of fetal tachycardia than the oral form.[29] If the arrhythmia recurs while on oral digoxin, an intravenous regimen of digoxin should be tried before starting other agents.

Digoxin is extensively distributed in tissues and is usually found in low plasma concentrations of 0.5 to 3.0 μg/mL. Although digoxin is also secreted in breast milk in similar concentrations as that found in the maternal steady-state serum concentration,[34] the total daily mammary excretion of digoxin in mothers with therapeutic serum concentrations is a minute amount that bears no pharmacologic significance to the infant. Indeed, Loughnan[34] demonstrated that the plasma of the nursing infant contained no detectable drug concentrations (limit of sensitivity 0.1 ng/mL) after 10 days of breastfeeding from a chronically digoxin-treated mother. Furthermore, assuming an infant milk intake of 150 mL per day, and based on the measured peak milk concentrations of digoxin, the investigator calculated that the average daily ingested amount is 1/100 of the maximum recommended daily dose of 12.5 μg/kg per day.

Consequently, to date, digoxin is considered safe in lactating mothers. Because experience with this drug in pregnancy is extensive, the use of digoxin could be preferable over other digitalis glycosides.

CLASS IA ANTIARRHYTHMICS

Quinidine

Quinidine is a class IA antiarrhythmic agent. Class I agents act by blocking sodium channels. IA compounds reduce Vmax and prolong the action potential duration. They are used in the treatment of ventricular and supraventricular arrhythmias, including those associated with Wolff-Parkinson-White syndrome.[35] Quinidine is also used for termination of atrial fibrillation/flutter. Quinidine has been used to treat pregnant women with ectopic rhythms from as early as the 1930s. Quinidine has also been used successfully, alone or in combination with other antiarrhythmics, for transplacental treatment of fetal supraventricular tachycardia[36] and fetal atrial flutter.[37] Its relative safety has been demonstrated repeatedly.[38]

Hill and Malkasian[39] described a 24-year-old gravida who was treated with 2400 g per day of quinidine throughout her pregnancy for idiopathic ventricular tachycardia. Serum quinidine levels averaged approximately 6 mg/L (therapeutic range, 4–6 mg/L) during this period. She had an uneventful pregnancy and delivered a full-term newborn in good condition by elective cesarean section. At the time of surgery, maternal and neonatal quinidine levels were equivalent, at 3.4 mg/L and 2.8 mg/L, respectively, indicating the drug readily crossed the placenta. Maternal serum and breast milk concentrations of quinidine measured 5 days postpartum were 9.0 mg/L and 6.4 mg/L, respectively, demonstrating that quinidine diffused freely into breast milk. The investigators also found high drug levels, within the toxic range, in the amniotic fluid before delivery, which they postulated to be secondary to spontaneous fetal voiding because 10% to 50% of unmetabolized quinidine is excreted by the kidneys.

There have been reports of adverse reactions of quinidine in the fetus, including thrombocytopenia, eighth nerve toxicity at much larger doses than those routinely used to treat arrhythmias, and minimal oxytocic effects.[40] Quinidine also depresses pseudocholinesterase activity by 60% to 70%, which could already be low secondary to gestation. This could create potential toxicity with the use of epidural or general anesthesia requiring ester-type anesthetics (procaine, tetracaine, chloroprocaine). Side effects are rare however. With respect to early fetal exposure, one surveillance study looked at 17 newborns exposed to quinidine during the first trimester.[41] Only one major birth defect was observed. There was no report of cardiovascular defects, oral clefts, spina bifida, polydactyly, limb reduction defects, or hypospadias.

At therapeutic concentrations, quinidine is approximately 60% protein-bound.[42] Changes in protein binding that occur during pregnancy will influence the free (unbound) portion of quinidine. Therefore, careful monitoring of maternal serum levels is necessary to avoid adverse effects. Quinidine is excreted in breast milk with a milk:plasma ratio of 0.31:0.71.[39] However, the amount likely to be ingested by the infant is considered to be far below the recommended pediatric dose. There are no contraindications to the use of quinidine in lactating mothers.[42a]

Procainamide

Procainamide is another class IA antiarrhythmic agent. It is synthesized by substituting an amide for the ester of procaine. Clinically, its action is similar to quinidine in that it is used to prevent or terminate supraventricular and ventricular arrhythmias. Procainamide can also be used to maintain sinus rhythm after cardioversion of atrial fibrillation/flutter that is unresponsive to quinidine or to prevent tachyarrhythmias associated with Wolff-Parkinson-White syndrome.[42]

There have been only a few reports documenting the safety and efficacy of procainamide in pregnancy. Dumesic and colleagues[43] described a successful intrauterine cardioversion of fetal supraventricular tachycardia by procainamide in whom digoxin alone and in combination with propanolol had failed to control. Maternal serum concentration at the time of delivery and neonatal concentration of procainamide were 15.6 mg/L and 4.3 mg/L, respectively.

In another report, the clinicians successfully cardioverted fetal supraventricular tachycardia resistant to digoxin and propanolol with a combination of procainamide and propanolol.[44] However, unlike the results reported by Dumesic et al.,[43] fetal levels of procainamide at delivery were found to be 30% higher than the maternal serum levels. The level of N-acetyl-procainamide (NAPA), the less active metabolite, in cord blood was also higher than in maternal serum, being 3.7 mg/L and 3.0 mg/L, respectively. Because fetal blood pH is slightly more acidic than placental pH, it can act to trap the weak base, procainamide, thereby limiting back diffusion.[44]

Battiste and colleagues[45] reported on a case of fetal supraventricular tachycardia causing hydrops fetalis at 17 weeks gestation, in which they successfully cardioverted using digoxin and procainamide with resolution of the hydrops. Sinus rhythm was maintained until term, and the patient delivered a normal male in good condition. This 17-week gestation fetus represents the earliest case of successful intrauterine cardioversion of fetal supraventricular tachycardia. Unlike the results obtained in previous reports,[43,44] maternal and cord blood levels of procainamide were equivalent, being 1.8 mg/L and 1.6 mg/L, respectively. NAPA levels in maternal and cord sera were likewise equal, at 2.4 mg/L and 2.2 mg/L, respectively.

Pittard and Glazier[46] demonstrated the translactal passage of procainamide and NAPA into breast milk. They found a mean milk:plasma ratio of 4.3 for procainamide and 3.8 for NAPA. Although the high ratio of milk:plasma suggests that both procainamide and NAPA accumulate in milk, the amount of drug transferred into milk is usually very low,[47] and the total daily amount ingested by an infant would not be expected to yield significant plasma concentrations. The Committee on Drugs of the American Academy of Pediatrics has found it unnecessary to discontinue procainamide treatment during lactation.[42a]

To date, procainamide has no known teratogenic effects.[40] It can be used with relative safety to treat a variety of maternal and fetal arrhythmias. However, because of the high incidence of the antinuclear antibodies and the lupus-like syndrome observed with chronic therapy, its use in long-term therapy should be reserved for patients who are refractory to or who do not tolerate quinidine.

Disopyramide

Disopyramide, a newer class IA antiarrhythmic drug, approved in 1977 for the treatment of ventricular arrhythmias, is similar in its electrophysiological properties to quinidine, possessing anticholinergic activity. Its clinical indications are also similar to quinidine and procainamide. It is as effective or better than the other 2 drugs in suppressing premature ventricular contractions (PVCs) and can have fewer gastrointestinal side effects.[42] It could also be useful in selected patients with ventricular tachycardia refractory to other agents. In Europe, it has been found to be equal in potency to quinidine in the prevention and termination of supraventricular arrhythmias.[48]

Disopyramide readily crosses the placenta.[40,49] Neonatal concentrations have been found to be approximately 40% of maternal concentrations. Disopyramide has not been demonstrated to be teratogenic in animal studies when given orally in doses $<$150 mg/kg body weight. However, low fetal weight was reported after higher dosing of the drug.[40,49]

Shaxted and Milton[49] described a 27-year-old pregnant woman with ventricular tachycardia who received 800 mg per day of the drug for 14 weeks until week 40 of pregnancy. She experienced no adverse effects and delivered a term infant with normal weight.

Leonard and coworkers,[50] however, described the initiation of premature labor associated with the use of disopyramide in a pregnant woman with cardiac arrhythmias secondary to mitral valve prolapse. The patient began to experience premature uterine contractions approximately 60 minutes after the initial oral dose. Uterine contractions recurred after each successive redosing, gradually subsiding after the drug was withdrawn. The mechanism of this oxytocic-like action of disopyramide is unknown.

Furthermore, Tadmor and colleagues[51] conducted a randomized, placebo-controlled, double-blind study in which 150 mg disopyramide was given every 6 hours for 48 hours for induction of labor in 10 pregnant women. Placebo was given to the other 10 women with the same indications in the control group. During the 48-hour study period, regular uterine contractions occurred in all 10 women in the study group, compared with none in the control group. Eight women delivered within 48 hours, compared with none in the control group. At delivery, the mean maternal:cord blood ratio of disopyramide was 0.36, compatible with the findings of Shaxted and Milton.[49] The authors suggest that perhaps the induction of uterine contractions could be related to a direct blockade of uterine β-receptors or to an increase in the plasma levels of labor-inducing agents such as oxytocin and PGE_2.

Abbi et al. reported on a case report of preterm labor and abruptio placentae after the administration of disopyramide.[52] A 26-year-old woman with Wolff-Parkinson-White

syndrome had recurrent episodes of supraventricular tachycardia refractory to medical therapy during the third trimester. She required repeated direct current cardioversion. The administration of disopyramide initiated painful uterine contractions and hemorrhage.

During the third trimester, Echizen and coworkers showed that the protein binding of disopyramide is decreased significantly.[53] As a consequence, there is an increase in the antiarrhythmic activity at the same therapeutic plasma concentration. With a therapeutic disopyramide maternal plasma concentration of 2.0 to 5.0 μg/mL, the mean fetal:maternal plasma ratio at term was 0.78. However, Ellsworth et al. treated a 27-year-old woman throughout pregnancy for ventricular fibrillation with an uneventful course and the fetal: maternal disopyramide plasma concentration ratio at delivery was 0.26.[54]

Disopyramide is excreted in breast milk. Barnett and colleagues[55] determined the plasma and breast milk concentrations in a nursing woman on 200 mg disopyramide 3 times daily. The mean milk:plasma ratio on days 5 through 8 was 0.9. This finding demonstrated the almost complete transfer of the drug from maternal blood into breast milk and is consistent with its physicochemical properties as a freely water-soluble compound with a low molecular weight and low binding to plasma proteins, thus facilitating its transfer from plasma to milk. The milk:plasma ratio for the N-monodesalkyl metabolite of disopyramide was 5.6. The infant showed no adverse effects and had undetectable serum levels of both disopyramide and active metabolite by the end of 4 weeks. The Committee on Drugs of the American Academy of Pediatrics considers the use of disopyramide compatible with breast feeding.[42a]

Because of limited experience regarding its use, and compelling evidence of its oxytocic properties, disopyramide should be used with caution during pregnancy because it could induce premature uterine contractions. It should be reserved for use in selected patients who do not respond to other antiarrhythmic agents.

CLASS IB ANTIARRHYTHMICS

Lidocaine

Lidocaine has been used primarily for epidural or local anesthesia during pregnancy. Investigators have shown that lidocaine rapidly crosses the placenta after intravenous or epidural administration.[56–58] After maternal administration, it can be detected in the umbilical cord in 2 minutes, and the maternofetal plasma concentration ratio is 0.5:0.7.[58] Snider and Way[59] were able to detect concentrations in the umbilical vein 6 minutes after maternal intravenous injection that were 55% of maternal levels. Other investigators have confirmed that fetal plasma concentrations at delivery are approximately 50% to 60% those of maternal levels.[60] A possible explanation that could account for the lower lidocaine concentration is that lidocaine is a weak base predominantly bound to α_1-acid glycoprotein whose fetal concentrations are approximately one third of maternal concentrations. This hypothesis is supported by Tucker et al.[58] who found lower binding capacity of lidocaine in fetal plasma. However, Snider and Way, in a second experiment,[61] demonstrated equal binding capacity in both maternal and fetal plasma. Brown and coworkers[60] showed that the elimination half-life of lidocaine in a neonate acquiring the drug in utero during maternal epidural anesthesia is approximately 180 minutes compared with 100 minutes in adults. There is evidence that the metabolism of lidocaine in the fetus and neonate is also hepatic.[62]

Snider and Way[59] studied 57 pregnant women who had levels of 3 mg/L. There was no gross evidence of central nervous system (CNS) toxicity when the fetal level was $<$2.5 mg/L. The therapeutic range in the nonpregnant state is 1 to 5 mg/L. If the maternofetal plasma ratio is approximately 0.5 to 0.6, maternal levels $<$4 mg/L are probably safe to avoid CNS toxicity. Data from the Collaborative Perinatal Project, which surveyed 293 of 50,282 mothers with lidocaine exposure during the first trimester, suggest that lidocaine administration during early pregnancy does not pose an increased risk of teratogenicity to the fetus.[40] Lidocaine toxicity after local lidocaine anesthesia has been reported in a small number of patients.[63,64] Kim and colleagues[63] described a case of accidental lidocaine injection into the fetal scalp during episiotomy. At delivery, the newborn demonstrated signs of severe toxicity, including apnea, hypotonia, fixed dilated pupils, and seizures. The fetal lidocaine level was 14 mg/L. The infant eventually recovered with completely normal follow up at 7 months.

Because lidocaine is a weak base, it could be trapped in the slightly more acidic fetal plasma compared with maternal plasma. Several studies have shown that in the presence of fetal acidosis, fetal drug concentrations of ionized weak bases such as lidocaine can be expected to be high, partly as a result of ion trapping and the increased transfer of lidocaine across the placenta.[56,65] Furthermore, acidosis can increase the unbound portion of lidocaine, facilitating further fetal trapping.[66]

Lidocaine transfer into breast milk during intravenous drug administration has been reported.[40] However, the total daily drug amount reaching the newborn is low and should be clinically insignificant. The Committee on Drugs of the American Academy of Pediatrics considers the use of lidocaine compatible with breastfeeding.[42a]

There are conflicting reports regarding whether lidocaine imposes deleterious neurobehavioral effects on the newborns. Some studies showed that it does not have adverse neurobehavioral consequences,[67] whereas others demonstrated that it does alter neurobehavioral responses at least in the neonatal period.[68]

There were 293 women identified in the Collaborative Perinatal Project that were exposed to lidocaine during the first trimester.[40] Although no teratogenicity was observed, there was a greater-than-expected incidence of respiratory tract anomalies (3 cases), tumors (2 cases), and inguinal hernias (8 cases). It is not known whether these findings were the result of lidocaine, maternal comorbidity, or are just incidental findings.

Despite the small amount of information of the actual use of lidocaine as an antiarrhythmic agent during pregnancy, data gathered from its clinical application as a local and epidural anesthetic agent indicate that it is relatively safe to use in pregnancy with careful blood monitoring. To avoid any possible side effects, fetal acid-base status should be within the normal range and maternal lidocaine blood levels should be kept within the mid to low therapeutic range. Because it is metabolized mainly by the liver, pregnant women with decreased hepatic flow should have their dosing regimen reduced accordingly.

Mexiletine

Structurally similar to lidocaine, mexiletine is a newer, oral class IB antiarrhythmic agent. It is well absorbed from the gastrointestinal tract. In fact, because it is absorbed almost completely from the proximal bowel, the delayed gastric-emptying that occurs in pregnancy could retard its absorption. Unlike lidocaine, mexiletine undergoes less than 10% first-pass hepatic metabolism, and bioavailability after oral administration is approximately 90%. It has a large and variable volume of distribution. Approximately 75% of the drug is protein-bound. Once in the circulation, it undergoes extensive metabolism in the liver, with approximately 10% to 20% excreted unchanged in the urine.[69]

There are little data regarding the safety of mexiletine in pregnancy. Animal studies in rats, mice, and rabbits receiving doses up to 4 times the maximum daily dose in humans found an increase in absorption in the fetus but no teratogenic effects. Timmis and coworker[70] described a 32-week pregnant woman who received 200 mg oral mexiletine 3 times daily and 40 mg propanolol 3 times daily for control of recurrent ventricular tachycardia. The patient underwent spontaneous vaginal delivery at 39 weeks and delivered a normal infant whose only problem was fetal bradycardia at 90 beats per minute. The infant's heart rate rose to 120 beats per minute 6 hours after birth and remained stable throughout the puerperium. The maternofetal ratio of mexiletine was 1.0, indicating complete placental transfer of the drug. Mexiletine was also secreted in breast milk. Timmis et al.[70] found milk:plasma ratios in the second postpartum day and 6 weeks postpartum to be 2.0 and 1.14, respectively. Although drug accumulation in breast milk is suggested by these data, the total daily amount ingested by the infant was minimal and therefore was not detectable in plasma. The Committee on Drugs of the American Academy of Pediatrics considers the use of mexiletine compatible with breast feeding.[42a]

Lownes and Ives[71] reported a 26-year-old woman who received 250 mg mexiletine 3 times daily and 50 mg atenolol per day throughout her conception, pregnancy, and postnatal course for ventricular tachycardia with multiple ectopic beats, which had been refractory to other drugs. She experienced premature rupture of membranes at 39 weeks and underwent induced labor followed by vaginal delivery of a small-for-gestational-age but otherwise normal and healthy male infant.

Mexiletine administration during pregnancy with no consequent adverse effects has been documented.[72] However, isolated reports of fetal bradycardia, a small size for gestational age, low Apgar scores, and neonatal hypoglycemia have been associated with its use.[71,72] Nevertheless, no teratogenic or long-term adverse effects have been observed in these or other reported cases.

Tocainide

There is little information regarding the adverse effects of tocainide during pregnancy. Common adverse effects occurring in approximately 30% of nonpregnant patients are gastrointestinal and neurologic in nature, including nausea, vomiting, dizziness, tremor, and paresthesia. Mental changes ranging from confusion to frank psychosis induced by tocainide have been reported.[73] Other less common adverse effects include elevated liver enzymes, hepatitis, acute pulmonary edema, and a rise in antinuclear antibodies with and without lupus. Agranulocytosis, rash and fever, interstitial pneumonitis, and cardiodynamic effects such as exacerbation of preexisting heart failure also have been reported.[74,75]

Studies in rats have demonstrated that tocainide administered in doses up to 300 mg/kg had no specific adverse effects on fertility, perinatal and postnatal development. No dysmorphogenic effects in the developing fetus were observed.[74] However, fetal abnormalities were reported in all test groups in a rabbit teratogenicity study. The incidence of toxicity differed significantly from control values at the highest dose level. Although maternal toxicity was observed, a drug effect on the fetus cannot be excluded.[75] In other animal experiments with rabbits given doses up to 4 times that for humans, and rats given 8 to 12 times the human dose, there is an increased incidence of abortions, stillbirths, fetal resorptions, and decreased neonatal survival.[76] To date, it is not known if tocainide is transferred into breast milk.

Because there is relatively little information regarding the use of tocainide in pregnancy, no recommendation for its use can be made at this time until there is more evidence documenting its safety.

CLASS IC ANTIARRHYTHMICS

Flecainide

Flecainide has been used with clinical effectiveness and safety to treat several cases of maternal tachyarrhythmias[77,78] and fetal tachycardias.[79–81] Flecainide readily crosses the placenta[78] with approximately 70% to 80% of the drug being transferred to the fetus.[78,80,81]

Wren and Hunter[79] first reported on a case of fetal tachycardia refractory to digoxin therapy, which was successfully cardioverted at 30 weeks gestation with intravenous flecainide for 5 minutes followed by oral therapy at 100 mg 3 times daily. A normal baby was delivered at 38 weeks. Maternal and cord plasma concentrations obtained simultaneously 5 hours after the last oral dose were 833 and 533 μg/L, respectively. Allan and coworkers[80] reported on the use of flecainide in the treatment of 14 cases of fetal atrial tachycardias associated with intrauterine cardiac failure. Twelve of the 14 fetuses were successfully cardioverted to sinus rhythm. One of the 12 fetuses subsequently died in utero. The remaining 2 fetuses who did not respond to flecainide therapy were successfully treated with digoxin. All newborns except one had good outcomes at 4 months of age. Comparison of maternal and cord serum concentrations demonstrated an approximate placental transfer of 80% with all fetuses possessing concentrations within the therapeutic range. Perry and colleagues[81] reported 2 cases of fetal tachycardia treated with flecainide. The calculated elimination half-life was 29 hours in the second fetus described. The investigators presented evidence to suggest that the fetus is capable of metabolizing the drug to avoid drug accumulation and toxicity.

Doig et al.[77] described a 24-year-old patient with twin gestations who developed incessant atrial tachycardia. Oral flecainide at 100 mg 3 times daily was administered when the patient failed verapamil and digoxin therapy. This treatment achieved only transient cardioversion to sinus rhythm. The patient spontaneously reverted to sinus rhythm during labor at 31 weeks of gestation, and 2 healthy infants were delivered vaginally by forceps. Wagner and colleagues[78] presented a 23-year-old woman with recurrent ventricular tachycardia and polymorphous premature ventricular beats who was being treated with 100 mg oral flecainide twice daily and 80 mg sotalol twice daily when she became pregnant. She continued with these medications throughout an uneventful pregnancy and eventually delivered a healthy baby by cesarean section 3 weeks before full term. The infant's follow up at 1 year was normal.

Thus, flecainide has become a treatment of choice for the treatment of fetal supraventricular tachycardia.[82] It is especially useful in treating cases refractory to digoxin and in those complicated by hydrops fetalis.[83] Although the majority of reported cases have good outcomes, caution is still advised with flecainide use because of the reports of death of 3 fetuses,[82,84] including one that died 15 minutes after transplacental administration.[82] None of these deaths, however, could be attributed with certainty to the drug.

The use of flecainide is compatible with breastfeeding. Wagner and coworkers[78] documented excretion of flecainide in human breast milk. Their calculated milk:maternal plasma ratios range from 1.57:1 to 2.18:1.

Propafenone

Brunozzi and colleagues[85] first described a 25-year-old pregnant patient with severe mitral insufficiency who was controlled with 300 mg propafenone 3 times daily for complex ventricular arrhythmias. Treatment started in the 20th week of gestation and continued throughout an uneventful pregnancy. The patient delivered a healthy infant by cesarean section at 36 weeks gestation. Placental transfer of propafenone and its active metabolite 5-OH propafenone, based on cord and maternal plasma concentrations, demonstrated an approximate 30% to 40% transfer. Libardoni and associates[86] reported on a 37-year-old woman treated with 300 mg propafenone 3 times daily starting in the 24th week for nonsustained ventricular tachycardia. The patient experienced no ill effects during the pregnancy and spontaneously delivered a healthy newborn at the 36th week. The investigators detected propafenone and 5-OH propafenone in both newborn plasma and maternal milk. Placental and milk transfer ratios were greater for 5-OH propafenone (0.42 and 0.50, respectively) than for propafenone (0.14 and 0.20, respectively), reflecting a difference in plasma protein binding of the 2 compounds to maternal plasma (approximately 75% vs. 95%). Although the infant was not breastfed, a hypothetical calculation of the total drug and metabolite ingested by the infant based on daily milk intake of 150 mg/kg body weight was well below the therapeutic range, at 0.03% of the maternal dose.

Although the use of class 1C antiarrhythmic agents has been described favorably in pregnancy, primarily for flecainide and propafenone, the absence of information gathered from controlled studies involving the use of these drugs during pregnancy and breastfeeding does not permit clear recommendations at this time.

CLASS II ANTIARRHYTHMICS: B-ADRENERGIC-BLOCKING AGENTS

β-Adrenergic-blocking agents act by blocking β1 and β2 receptors. Cardiac effects are mediated primarily by β1 receptors while β2 receptors are found in the bronchi and the blood vessels. β2-receptor-mediated myometrial relaxation also occurs in pregnancy. Nonselective β-blockers include propranolol, nadolol, pindolol, timolol, sotalol, carvedilol, and labetalol (carvedilol and labetalol also have α-blocking activity); β1-selective antagonists include atenolol, metopro-

lol, and esmolol (available in intravenous form). β-blockers are useful in the management of supraventricular and ventricular tachycardia. They are also used to control the rate of ventricular response in atrial flutter and atrial fibrillation. The antiarrhythmic effects of these agents have been attributed to the β-adrenergic-blocking activity rather than the membrane-stabilizing properties possessed by some of these agents.[87]

Although no systematic study has been conducted to assess the treatment of β-blockers for arrhythmias during pregnancy, growing documentation of their use in the past few years has accumulated with regard to treatment of pregnant patients with hypertension,[88,89] the hereditary long QT syndrome,[90] thyrotoxicosis,[91] idiopathic hypertrophic subaortic stenosis,[92] and fetal tachycardia.[93] To date, none of the β-blockers has been implicated as a causative agent of fetal malformation. At least 2 studies included women on β-blocker therapy before conception and no fetal abnormalities were observed in both studies.[88,94] Both nonselective and selective β-blockers readily cross the placenta.[95] At delivery, similar serum drug concentrations are found in the mother and the umbilical cord, although lower fetal concentrations than maternal concentrations have been reported. The effects of α and β-adrenergic receptor stimulation and blockade on maternal–fetal physiology are shown in Table 2.

Propranolol

Propranolol is the most commonly used β-blocking agent during pregnancy. After an oral dose, it is essentially absorbed completely from the gastrointestinal tract. First-pass effect ranges from 20% to 40%. Peak plasma concentrations are reached within 90 minutes and duration of action ranges from 6 to 12 hours. Propranolol is a weak base, which is >90% protein-bound. It undergoes extensive metabolism with a minor amount of unchanged drug excreted by the kidneys. Pregnancy has no effect on the maternal clearance, volume of distribution, elimination half-life, and the area under the concentration–time curve of propranolol.[96]

In the past 3 decades since the clinical introduction of propranolol, there are numerous reports favorably documenting its use in pregnancy.[88,92,94,97,98] However, adverse fetal effects have been described, including bradycardia,[99] birth apnea,[100] hypoglycemia,[99] intrauterine growth retardation (IUGR),[99,101,102] hyperbilirubinemia,[99] polycythemia,[99] prolonged labor,[99] and a single case of fetal death.[103] None of these complications, however, were reported consistently in chronic therapy studies. In a retrospective study, Pruyn and coworkers[101] observed that 10 of 11 babies exposed to long-term propranolol in utero had weights and head circumferences below the 50th percentile. They postulated that decreased umbilical blood flow seen in pregnant ewes[104] could deprive the growing fetus of essential nutrients and therefore retard growth. However, prospective clinical studies have shown the incidence of IUGR associated with propranolol use to be approximately 4%,[88,94,105] with normal-sized babies delivered in later pregnancies despite continued propranolol therapy.[105] Consequently, it would be inappropriate to conclude that β-blockers are commonly associated with IUGR. In women with the long QT syndrome, it was shown that the immediate postpartum period is associated with a sharp increase in the risk of cardiac events. It is advised not to discontinue β-blockers during pregnancy in this condition and throughout the postpartum period.[90]

Tunstall[100] observed that administration of 1 mg intravenous propranolol in 3 pregnant patients before cesarean section led to a 5- to 6-minute delay in spontaneous respiration of all babies, 2 of which required brief intubation. A subsequent random double-blind study found this complication in all babies whose mothers required preoperative propranolol, although the outcome was ultimately normal beyond the first 10 minutes of birth. The investigators postulated that β-blockade of the cervical sympathetic discharge might have been an etiologic factor. Cottrill and colleagues[106] described a case of neonatal transient apnea, bradycardia, and hypoglycemia observed in a pregnant patient on 160 mg propranolol daily, increasing to 240 mg the day before delivery, with an additional 3 mg given parenterally 1 hour before cesarean section. Neonatal drug concentrations 4 hours postpartum were more than twice the cord concentration measured at delivery. Although others have

TABLE 2. Adrenergic Influences on Maternal–Fetal Physiology

	Stimulation		Blockade	
	α Receptor	**β Receptor**	**α Receptor**	**β Receptor**
Fetal heart rate	↔	↑	↔	↔↓
Mother heart rate	↔	↑	↔	↓
Umbilical blood flow	↔	↑	↔	↓
Myometrial activity	↑	↓	↓	↑

↔ no effect; ↑ increases; ↓ decreases.
Reprinted with permission from Widerhorn J, Rubin JN, Frishman WH, et al. Cardiovascular drugs in pregnancy. *Cardiol Clin.* 1987; 5:651–674.

reported similar adverse effects, no lasting consequences were detected in any child.[99,106]

Excretion of propranolol in breast milk has been reported by a number of investigators. Karlberg and colleagues[107] found that 3 hours after breastfeeding, the milk: maternal plasma ratio is approximately 1, and that the excretion of propranolol into breast milk appeared to be dose-dependent. Bauer and coworkers[108] found that propranolol concentrations in breast milk were less than 40% and 64%, respectively, of peak plasma concentrations after a single dose of 40 mg and continuous dosing of 40 mg 4 times daily. They estimated that a nursing infant ingesting 500 mL of breast milk from a mother receiving a total daily dose of 160 mg would have an accumulative dose of 21 mg over 24 hours, far below the usual therapeutic range. Other studies[97,98] also have demonstrated that propranolol is transferred into breast milk in amounts that would be unlikely to cause adverse effects in the infant.

Nadolol

Nadolol is a nonselective β-adrenergic-blocking agent indicated for the treatment of hypertension and angina. It has a long serum half-life (20 to 24 hours).[109] There is limited experience with nadolol in pregnancy. Fox et al. reported a case of a mother treated for IgA nephropathy and hypertension with nadolol (20 mg per day), triamterene, and hydrochlorothiazide.[110] An emergency cesarean section at 35 weeks produced an infant who was small for gestational age with respiratory depression, bradycardia, hypoglycemia, and hypothermia. Although the maternal disease and the diuretic could have contributed to these complications, the long duration of action of nadolol, its renal elimination, and low protein binding (30%) might predispose the fetus and the newborn to toxic side effects. Propranolol would be a more desirable drug in pregnancy because of its shorter half-life and extensive protein binding (90%). Nadolol is excreted in breast milk and is found in concentrations 4.6 times that of the serum concentration in women taking 80 mg of nadolol daily.[111] However, it is estimated that only approximately 2% to 7% of the therapeutic pediatric dose would be ingested by the infant in a day. The American Academy of Pediatrics considers nadolol to be compatible with breast feeding.[42a]

Pindolol

Pindolol is only one of 2 β-blockers that received a U.S. Food and Drug Administration (FDA) pregnancy risk classification of a B, the other being acebutolol. It is a nonselective β-receptor antagonist with pronounced intrinsic sympathomimetic activity. Pindolol crosses the placenta with cord to maternal serum ratios at 2 and 6 hours after the last dose equal to 0.37 and 0.67, respectively.[112] There have been no reports describing fetal malformations with pindolol use in pregnancy. Pindolol causes no changes in utero- or umbilicoplacental vascular impedance or blood flow, has no effect on fetal hemodynamics, and does not affect fetal cardiac function.[113] Clinical evidence of β-blockade has not been reported in the offspring of mothers taking pindolol during pregnancy. In a comparative study with methyldopa, blood pressure was found to decrease more significantly with pindolol with no difference in fetal intrauterine growth, Apgar scores, and fetal morbidity.[114] No significant difference with respect to Apgar score or neonatal complications was found when pindolol was compared with acebutolol and atenolol.[115] The pindolol group did have higher birth weights than the other 2 β-blocker treatment groups (3375 g vs. 3160 g versus 2745 g, respectively). The manufacturer states that pindolol is secreted in human milk.[116] However, no published reports are available that describe the use of pindolol during human lactation or the amount excreted.

Metoprolol

Metoprolol is a selective β_1-adrenergic antagonist with low lipid solubility that theoretically would not interfere with β_2-mediated vasodilation and bronchodilation or its effect on uterine tone. Metoprolol readily crosses the placenta with cord concentrations approximating those in maternal blood at delivery.[117] Lindeberg and coworkers[117] studied 101 pregnant patients with systemic hypertension treated with metoprolol alone or in combination with hydralazine and a diuretic for 4 weeks during pregnancy. This group was compared with 97 hypertensive pregnant patients treated with hydralazine. Perinatal mortality and fetal growth retardation were lower in the metoprolol group. No significant adverse effects were reported in the fetus. Hogstedt and coworkers[118] also showed that induced increase of metoprolol metabolism by the hepatic monooxygenase system is pregnancy-related. Similarly, metoprolol has been shown to induce cytochrome P4502D6 activity in pregnancy, leading to increased clearance of the drug.[15]

Frigo et al. reported on a case of a 29-year-old woman who developed supraventricular tachycardia resistant to digoxin and verapamil 24 hours after starting tocolytic treatment with intravenous hexoprenaline.[119] Treatment with metoprolol finally converted the patient to sinus rhythm. There was no observed adverse effect on fetal heart rate or umbilical cord blood flow. The use of β-blockers in general should be avoided in hypertensive mothers who are likely to give birth to very-low-birth-weight infants because of the poor outcomes seen with the use of metoprolol or atenolol in these circumstances.[120]

Investigators have shown that metoprolol accumulates in breast milk in concentrations 3 to 4 times greater than the mean plasma concentration.[109,117] This can be interpreted as the "ion trapping" effect of milk for weak basic compounds like β-blocking agents because it has a slightly lower pH than blood. However, it has also been demonstrated that plasma

concentrations of metoprolol in the nursing infant are very low or undetectable.

Atenolol

Atenolol is another β_1-blocker with low lipid solubility and a relatively long half-life. It also rapidly crosses the placenta.[109] Rubin and colleagues[121] conducted a prospective, double-blind, randomized trial involving atenolol use in 120 hypertensive pregnant patients. They reported identical Apgar scores and birth weights in both control and study groups. Transient bradycardia with no long-lasting adverse effects was more common in the atenolol-treated group. However, the atenolol-treated group had fewer cases of hypoglycemia, respiratory distress, and death. Reynolds and coinvestigators[122] performed a similar prospective, double-blind, randomized study involving 120 gravidas who developed hypertension during the third trimester. The children were followed for 1 year postnatally with no short- or medium-term adverse effects observed. However, several other controlled studies have demonstrated reduced birth weights in newborns of mothers taking atenolol compared with placebo or other β-blockers such as pindolol, acebutolol, and labetalol.[109,123] This could be explained by atenolol's ability to decrease the peripheral vascular resistance of both sides of the uteroplacental circulation, resulting in decreased placental perfusion and growth retardation. In addition, markers of placental well-being such as placental lactogen concentration and weight are both decreased during atenolol treatment.

There has been one case report of a retroperitoneal fibromatosis in a fetus whose mother took 100 mg atenolol daily from the second month to the end of pregnancy.[124] The retroperitoneal localization of the tumor is similar to that of fibroses reported in adults after exposure to atenolol. The tumor was treated with antimitotics until 3 months of age and disappeared by the age of 4, but severe scoliosis was present.

It was shown that resting and exercise heart rates are higher in the third trimester with atenolol therapy than at postpartum, despite similar blood levels of drug. These findings suggest a need for more β-blocker to be given during gestation for heart rate control.[125] When given to women considered to be at risk for preeclampsia, atenolol was shown to decrease the incidence of preeclampsia from 18% to 3.8%.[126]

Atenolol has been demonstrated to accumulate in breast milk in concentrations higher than those of maternal plasma.[109] Because it is a weak base, this is consistent with the "ion trapping" concept. All these studies agree that infants breastfed by atenolol-treated mothers demonstrated negligible plasma drug levels.

In summary, atenolol provides good blood pressure control and is well tolerated in both the mother and the fetus. Fetal outcome also improves with therapy. However, chronic therapy and therapy in the first trimester should be avoided because it could result in low birth weight.[127]

Acebutolol

Acebutolol is the only β_1-adrenergic selective receptor blocker with a FDA pregnancy risk classification of a category B. It has some intrinsic sympathomimetic activity. Acebutolol crosses the placenta, and there is some evidence that the fetus metabolizes acebutolol to diacetolol in utero.[109] In a comparative study with methyldopa, no difference was found between the 2 drugs with respect to premature labor, live births, birth weight, placental weight, or fetal distress, and no incidence of hypoglycemia or bradycardia were reported.[128] There is also no significant difference with respect to Apgar score or neonatal complications when acebutolol is compared with pindolol and atenolol.[129] The pindolol- and acebutolol-treated infants' mean birth weight, however, was somewhat higher than that of the atenolol-treated infants. Because of the extended plasma half-life of the metabolite, acebutolol's effects are long-lasting, and hence careful monitoring of the neonate is required.[109] The effects on blood pressure and respiration after delivery could last up to 3 days. Furthermore, acebutolol is concentrated in breast milk, and pharmacologically active amounts of acebutolol and diacetolol might be received by a neonate if the daily maternal dosage exceeds 400 mg per day and/or renal function in the mother is impaired.[129]

Esmolol

Esmolol is a β_1-adrenergic receptor blocker that has been used in pregnancy to control heart rate in thyrotoxicosis, to treat blood pressure elevation, and to treat supraventricular arrhythmias.[109] It has a rapid onset of action and maximum effect (within 5–10 minutes), a plasma half-life of only 9 minutes, and a duration of action lasting 20 minutes. Esmolol has a rapid transplacental passage, and its administration lowers both maternal and fetal heart rate.[109] However, the heart rate returns to normal once the drugs is discontinued. In one case report, esmolol was successfully used to convert a maternal paroxysmal supraventricular tachycardia to sinus rhythm at the time of delivery.[130] The Apgar scores of the neonate were 7 and 9 at 1 and 5 minutes, respectively. Also reported was a weak cry, poor muscle tone, a heart rate of 120 beats per minute, and a respiratory rate of 40 breaths per minute. The infant became jaundiced at 48 hours, but by 60 hours the respiratory rate, cry, and muscle tone returned to normal. At 6 weeks and 6 months follow up, the baby remained healthy. Thus, caution and fetal monitoring must be exercised whenever esmolol is used for a pregnant patient. It is unknown if esmolol is excreted into breast milk.[116]

Sotalol

Sotalol is a nonselective β-adrenergic antagonist with class III electrophysiological properties. After an oral dose, it

is completely absorbed from the gastrointestinal tract with almost 100% bioavailability. Sotalol is poorly protein-bound. Peak plasma concentration is achieved in 2 to 3 hours and the elimination half-life is 10 to 12 hours. It is excreted unchanged in the urine. Its has been used in pregnancy to manage chronic hypertension and maternal and fetal arrhythmias. Third-trimester pharmacokinetics demonstrated a plasma half-life of 11 and 7 hours after a single oral and intravenous dose of sotalol, respectively, similar to the half-life obtained 6 weeks postpartum.[131] Drug clearance was significantly greater in the third trimester, but the volume of distribution did not change compared with postpartum. Sotalol readily crosses the human placenta.[131]

O'Hare and coworkers[131] administered sotalol to 12 hypertensive pregnant women in increasingly titrated doses starting at 200 mg and found that the drug effectively reduced blood pressure at a mean daily dose of 433 mg. At delivery, cord concentrations approximated maternal plasma concentrations. Eight of 12 liveborns were normal. Of the other 4, 2 died of congenital anomalies, 1 had perinatal asphyxia, and 1 mild transient hypoglycemia. Sotalol was started in the mid-second trimester so it could not be implicated in the 2 cases of congenital anomalies. The other complications did not pose long-lasting adverse effects.

Transplacental therapy with sotalol has been used to treat fetal supraventricular tachycardia (SVT). In one study, 14 fetuses identified with SVT diagnosed at gestational ages ranging from 24 to 35 weeks were first treated with digoxin before oral sotalol (80–160 mg × 2) was given to the mother.[132] Cardioversion was obtained in 10 fetuses. Two of the nonresponding fetuses did not cardiovert even after using a different combination of digoxin, sotalol, flecainide, and/or propafenone after birth. These fetuses were found to have a long ECG RP interval tachycardia. In another study looking at 43 fetuses with perinatal atrial flutter, digoxin failed to prevent recurrence of atrial flutter at the time of delivery in one fourth of the patients, whereas no recurrence of atrial flutter was reported in the sotalol group.[133]

Transfer of sotalol into breast milk was documented from 5 breastfeeding mothers. Sotalol accumulated in breast milk with a mean milk:plasma ratio of 5.4:1. Although the calculated total drug dose in a breastfeeding infant ingesting 500 mL of milk did overlap with the therapeutic range, no β-blockade effects such as bradycardia were observed. Hackett and colleagues[134] assayed sotalol levels in the breast milk of a 22-year-old woman. They found similar a serum drug maternal:fetal ratio at delivery and milk:plasma ratios compared with those measured by O'Hare et al.[131]

Summary

Although there are a few documented reports describing adverse fetal outcomes such as IUGR,[127,135] bradycardia, hypoglycemia, apnea, and hyperbilirubinemia associated with the use of β-blockers (especially propranolol) during pregnancy, the incidence of these complications is low enough to allow the general conclusion that β-blockers can be used with relative safety during pregnancy. Higher doses might need to be used to control heart rate during pregnancy despite adequate drug blood levels, suggesting a decreased sensitivity to the effects of β-blocker therapy.[125] Most β-blockers have been shown to accumulate in breast milk in concentrations 4 to 5 times higher than maternal plasma levels. This can be explained by the slightly more acidic breast milk acting as an "ion trap" for β-blockers, which are weak bases. However, because the amount of milk consumed daily by an infant is low, the amount of drug transferred is clinically insignificant. Consequently, mothers on β-blocker therapy can continue breastfeeding with relative safety.

Finally, Hurst and coworkers make the following recommendations when using β-blockers in pregnancy[109]:

1. Try, when possible, to avoid initiating long-term therapy during the first trimester.
2. Use the lowest dose possible. The use of adjunctive antihypertensives might help achieve this goal.
3. Discontinue, if possible, therapy at least 2 to 3 days before delivery to limit the drug's effect on uterine contractility and to prevent possible neonatal complications.
4. Neonates born to mothers on β-blockers should be closely observed 72 to 96 hours after parturition unless the drug was stopped well before delivery.
5. To avoid the interference with β_2-mediated uterine relaxation and peripheral vasodilation, blockers with β_1-selectivity, intrinsic sympathetic activity, or α-adrenergic-blocking activity are preferred.
6. Mothers should avoid nursing their infants at the time of expected peak maternal β-blocker plasma concentrations, usually occurring 3 to 4 hours after a dose.

CLASS III ANTIARRHYTHMICS

Amiodarone

After an oral dose, the absorption of amiodarone is slow, incomplete, and unpredictable. Approximately half of the dose is absorbed. Peak plasma concentrations are reached in 2 to 10 hours, but therapeutic steady-state levels could require up to 4 weeks. Amiodarone, being lipophilic, has a large volume of distribution and accumulates mainly in adipose tissues. Nevertheless, drug deposits can be found in nearly every type of tissue, including skin, cornea, and liver. It undergoes hepatic metabolism with approximately 1% of the dose excreted unchanged in the urine. Biliary excretion of hepatic metabolites is also involved. The main metabolite is desethylamiodarone (DEA). The elimination half-life ranges from 13 to 100 days, with an average of 40 to 50 days. Approximately 96% of the drug is protein-bound.

Transplacental passage of amiodarone and its main metabolites have been documented in numerous reports.[136–138] McKenna and coworkers[136] treated a 34-week pregnant woman who had paroxysmal atrial flutter–fibrillation associated with the Wolff-Parkinson-White syndrome resistant to quinidine. She was started with a loading dose of 800 mg amiodarone daily for 1 week followed by a maintenance dose of 400 mg daily. She delivered at 41 weeks a normal healthy infant who had no complications except for a sinus bradycardia of 104 to 120 beats per minute, which persisted for 48 hours immediately postdelivery. At birth, the neonatal levels of amiodarone and DEA were approximately 25% of those in maternal plasma. Pitcher and colleagues[137] reported similar results of transplacental transfer, 10% of amiodarone and 25% of DEA, when they successfully treated a patient with atrial tachycardia resistant to multiple drugs in the last 3 weeks of her pregnancy. Both mother and child had no complications. Arnoux and coworkers[138a] successfully treated refractory fetal tachycardia in a 31-week pregnant patient with amiodarone loading dose 1600 to 1200 mg daily for 1 week followed by 800 mg daily for 6 weeks, and digoxin 0.25 mg per day. The mother delivered an infant with no neonatal complications except for transient hypothyroidism that normalized 1 month postdelivery. The investigators noted that neonatal levels of amiodarone and DEA were 12.7% and 19.6% of maternal levels, respectively, regardless of dosage, and that a linear relationship existed between plasma concentrations and the dose administered. They suggested that maternal levels would serve as a good indicator of plasma levels. Gembruch and colleagues[138] described another case of refractory fetal supraventricular tachycardia with hydrops fetalis in a 24-week pregnant patient. It was successfully treated with repeated intravascular injections of amiodarone into the umbilical vein at doses of 10, 20, and mostly 40 mg when maternal intravenous therapy failed to produce adequate fetal drug concentrations. A small-for-gestational-age infant was delivered by cesarean section at 37 weeks with normal thyroid function.

Reports have documented amiodarone therapy early in gestation with no consequent adverse effects.[139–140a] Penn et al[139] reported on a case in which an amiodarone loading dose of 800 mg daily for 1 week and a maintenance dose of 200 mg daily were administered to a 16-week pregnant woman. She delivered a normal baby in the 39th week who had some initial QT prolongation that normalized in 7 weeks. Umbilical cord concentrations of amiodarone 9 hours after the last maternal dose were approximately 9% of those of maternal serum. Robson and associates[141] reported on 2 cases, the first in which they maintained a patient on amiodarone 200 mg per day for atrial fibrillation associated with mitral stenosis throughout her pregnancy from conception to delivery. She delivered a healthy normal infant. At birth, amiodarone and DEA levels in cord plasma were approximately 10% and 19% of maternal levels, respectively. In the second case, they treated a 22-week-pregnant patient for paroxysmal atrial tachycardia with 400 mg amiodarone per day and 50 mg metoprolol per day. She delivered in the 39th week of gestation a healthy male infant. Again, transplacental transfer of amiodarone and DEA approximated 10% and 20%, respectively. Valensise and coworkers[140] described 2 pregnant sisters, ages 24 and 26, with familial dilatative cardiomyopathy and malignant ventricular arrhythmias who were treated with 200 to 400 mg amiodarone per day since the beginning of pregnancy. The 2 mothers experienced no adverse effects and delivered healthy normal infants with normal thyroid function.

The high content of iodine in amiodarone, approximately 40% of its molecular weight, has been implicated in causing fetal hypothyroidism in a number of pregnant women receiving amiodarone therapy.[141–146] DeWolf and colleagues[142] described a case of severe congenital hypothyroidism with goiter and growth retardation associated with maternal ingestion of 200 mg amiodarone daily from the 13th week of pregnancy. The infant required hormonal replacement until age 20 months. Widerhorn and colleagues[143] reviewed the literature up to 1991 regarding the adverse effects of amiodarone in pregnancy and found 9% incidence of hypothyroidism, similar to that reported for amiodarone-induced hypothyroidism in the adult population. A Canadian historical cohort study of amiodarone exposure in gestation conducted by Magee and coinvestigators[145] also found a 9% (1 of 12 cases collected) incidence of hypothyroidism. A similar incidence was found for hyperthyroidism. The hypothyroid infant was supplemented with 0.05 mg oral L-thyroxine daily for 5 months postdelivery, and thyroid function normalized by 7 months of age. Interestingly, the mother's second pregnancy resulted in the birth of a euthyroid child, despite identical maternal drug therapy for 400 mg amiodarone for 5 days per week in conjunction with a β-blocker. DeCatte and coworkers[146] described a case of persistent fetal supraventricular tachycardia detected in a 26-week pregnant patient. Transplacental and direct fetal administration of amiodarone caused hypothyroidism in week 28 detected by measuring thyroid hormone levels drawn through cordocentesis. Intraamniotic instillation of 250 mg L-thyroxine weekly for 3 weeks gradually restored fetal free T4 and thyroid-stimulating hormone (TSH) levels. A male infant was delivered at 37 weeks by cesarean section. The neonatal electrocardiogram showed Wolff-Parkinson-White syndrome controlled by digoxin alone. At the time of report, the baby was developing normally with normal thyroid function. Matsumura and colleagues[147] studied neonatal outcome in 9 pregnant women treated with 200 mg amiodarone per day for resistant tachycardia. All women were clinically euthyroid in the third trimester. At birth, 8 of 9 newborns had normal or borderline-normal values of T4 and TSH measured on dried

umbilical blood spots. Only one neonate presented clearly abnormal values of T4 and TSH (96 mU/L), which normalized within 1 month after birth. Clinically, all infants appeared normal with no goiters. Follow ups at 3, 6, and 12 months were reported as normal for all infants.

A review of 34 pregnancies that involved maternal amiodarone treatment found no adverse effects in 53% of neonates and minor side effects, which included bradycardia and prolonged QT interval, in 15%.[143] Twenty-one percent were small for gestational age, 12% were premature, and 9% had prenatal hypothyroidism. Other adverse neonatal effects such as IUGR, motor and neurologic developmental abnormalities, and ventricular septal defect have also been reported.[143,144,146,148] Magee and coworkers[149] looked at the long-term neurodevelopment in children exposed to amiodarone during gestation. There was no difference in IQ scores between the 8 amiodarone-exposed toddlers and the matched controls. However, the exposed toddlers showed expressive language skills that were relatively poorer than the verbal skills when compared with controls. The 2 older amiodarone-exposed children (aged 9.7 and 12) had good global IQ scores and social competence but had problems with reading, comprehension, written language, and arithmetic. They had a clinical picture similar to that described in the Nonverbal Learning Disability Syndrome. Bartalena et al. also looked at the neurodevelopment of 11 transiently hypothyroid amiodarone-exposed infants and found mild abnormalities also reminiscent of the Nonverbal Learning Disability Syndrome.[150] These features were also reported in some euthyroid-exposed infants. This suggests that there might be a direct neurotoxic effect of amiodarone during fetal life. However, Grosso and colleagues did a follow-up evaluation of 2 children (approximately 5-year-old) exposed during gestation to amiodarone who also developed transient neonatal hypothyroidism.[151] They had normal psychomotor development with normal verbal and performance IQ scores.

Several reports have shown that amiodarone accumulates in relatively high concentrations in milk.[40,136] McKenna and coworkers[136] found that at 9 weeks postpartum, the milk:plasma ratio ranged between 2.31 and 9.21. The authors estimated the amount of drug exposed to an infant at this stage of development is equivalent to doses of approximately 100 mg per day in a 70-kg man, a relatively low maintenance dose. Strunge and coinvestigators[140a] described an 18-year-old woman receiving 200 mg amiodarone daily throughout her pregnancy and nursing. They also observed relatively high levels of amiodarone in milk, but not in amounts high enough to cause amiodarone levels to exceed 0.1 mg/mL in the infant serum.

In view of the conflicting literature regarding the adverse effects of amiodarone used in pregnancy, and until experience with its use is documented more widely, it should be used with great caution in pregnancy. Because of the potent side effects, which include neonatal hypothyroidism, hyperthyroidism, bradycardia, small size for gestational age, prematurity, and possibly neurodevelopmental problems, it should be used as a second-line drug in cases resistant to those antiarrhythmic agents whose safety has been more established. Physicians using amiodarone in pregnant women should be wary of possible thyroid dysfunction, and fetal thyroid hormone levels should be monitored regularly. Although a couple of reports have shown that the nursing infant's serum levels of amiodarone are not high enough to cause toxicity, because of high accumulation of the drug in breast milk, amiodarone therapy in a nursing mother is not recommended.

Bretylium

There is only one case report in the literature regarding oral bretylium use during pregnancy and breastfeeding. Gutgesell and colleagues[152] described a 39-year-old woman with a long QT interval syndrome who was being treated with oral bretylium and atenolol for ventricular arrhythmias when she became pregnant. She continued receiving 400 mg bretylium every 8 hours, 25 mg atenolol at bedtime, and 20 mg propanolol 3 times daily for migraines throughout an uneventful pregnancy. She spontaneously delivered a healthy infant at term who experienced no complications except for transient mild hyperbilirubinemia, which was attributed to mild ABO incompatibility and "breast-milk jaundice." Placental transfer and breast milk transfer of bretylium were not documented because blood and breast milk assays for the drug were not available at the time. The child had a normal follow up at 4 months.

Because so little information is known currently regarding the safety of bretylium use in pregnancy, no recommendations can be made at this time.

CLASS IV ANTIARRHYTHMICS: CALCIUM CHANNEL ANTAGONISTS

Verapamil

Verapamil is very effective in the cardioversion of paroxysmal supraventricular tachycardia to sinus rhythm and is also useful in slowing the ventricular response during atrial fibrillation or flutter. Verapamil has been reported to be successful in the management of maternal supraventricular arrhythmias,[153,154] in the treatment of severe maternal hypertension,[155,156] preeclampsia,[157] premature labor,[158] and fetal supraventricular tachycardias.[158–160] None of these cases reported adverse pregnancy or fetal outcomes.

Byerly and colleagues[153] described a 22-year-old woman at 6½ months gestation who presented to the emergency room with paroxysmal supraventricular tachycardia.

After multiple failed attempts of cardioversion by Valsalva maneuver and carotid massage, conversion to sinus rhythm was achieved with 10 mg intravenous verapamil administered over 10 minutes in 2 5-mg boluses. The patient returned to the emergency room 1 week later with the same complaint and again was successfully cardioverted using the identical drug therapy. She completed an uneventful pregnancy and delivered a normal full-term infant without difficulty 3 months later. Klein and Repke[154] reported a similar case of a late third-trimester gravida who was successfully treated for paroxysmal supraventricular tachycardia with a single dose of 5 mg intravenous verapamil and subsequently had a normal delivery and neonatal outcome.

The effects of chronic therapy with verapamil have been studied by Orlandi et al.,[155] who conducted a case-control study in which 120 mg verapamil in an oral slow-release form 3 to 4 times daily was given to 90 hypertensive gravid women. Dihydralazine was added to 39 patients for improvement of blood pressure control. They observed a significant fall in systolic and diastolic blood pressure in the hypertensive group, and also observed significantly lower birth weights of infants in the hypertensive group with recovery of growth in 15 growth-retarded fetuses. No significant side effects were recorded in the mothers, fetuses, and newborns, and the duration of labor did not differ between the 2 groups. They concluded that verapamil alone or with dihydralazine appears to be safe and effective for the treatment of hypertension during pregnancy.

Kleinman and coworkers[160] reported their experience in successfully treating 6 cases of in utero fetal supraventricular tachycardia in the third trimester with a combination of digoxin and verapamil therapy. One of the 6 patients developed maternal second-degree atrioventricular block necessitating discontinuation of verapamil. All patients had increased digoxin serum levels with concomitant verapamil therapy requiring adjustment of the digoxin dosage. The transplacental transfer of verapamil was demonstrated at approximately 30% to 40% of maternal levels 6 to 8 hours after the last oral dose with chronic oral therapy.[160] All neonates received antiarrhythmic prophylaxis with digoxin for 1 year after birth, and none demonstrated abnormal electrocardiographic findings or other adverse outcomes.

The effects of verapamil in nursing mothers has also been reported. Andersen and colleagues[161] calculated a serum verapamil level of 2 μg/L in a nursing infant, which is $<0.1\%$ of the administered maternal dose and consequently deemed negligible. Miller and coworkers[162] reported an average drug transfer of 64% into breast milk but could not detect drug levels in the infant plasma. In contrast, Inoue et al.[160] measured drug levels 10-fold higher in breast milk, at 300 μg/L, than those measured by Anderson et al.,[161] and cautioned against breastfeeding while on verapamil therapy.

Diltiazem

Diltiazem is another calcium-channel blocker whose electrophysiological action is similar to verapamil. To date, there are no reported adverse effects of diltiazem use in human pregnancy. Several animal studies have documented the effective tocolytic properties of diltiazem.[164,165] Significant reduction in mean blood pressure with little change in heart rate was also observed.[164,165] Adverse effects such as embryo and fetal deaths, decreased neonatal survival rates, and skeletal abnormalities were observed in mice, rats, and rabbits given doses 5 to 10 times greater than the recommended human daily dose based on a milligram per kilogram weight basis.[76]

Excretion of diltiazem into breast milk was reported by Okada and colleague[166] in a woman receiving 60 mg diltiazem 4 times daily. The investigators observed similar maternal plasma and milk concentrations, indicating that the drug is transferred freely into milk on the fourth day of treatment. Peak milk concentrations exceeded 200 μg/L.

Nifedipine

Nifedipine is a lipophilic dihydropyridine derivative, which differs from the other calcium-channel antagonists, verapamil and diltiazem, in possessing a potent vasodilating effect on vascular smooth muscle and minimal effects on the cardiac conducting system in vivo.[167] It significantly reduces the vascular resistance of both systemic and pulmonary circulations. Up to a 20% decrease in diastolic and mean arterial pressures is observed after administration of nifedipine. Mean pulmonary arterial pressure also falls. The vasodilating effect is more prominent in hypertensive patients than normotensive ones. The drop in vascular resistance leads to an increase in cardiac output. When nifedipine is given rapidly, reflex tachycardia can occur secondary to systemic vasodilation.

Nifedipine and its indications in pregnancy have been reviewed in detail by Childress and Katz.[168] The authors found that nifedipine has demonstrated safety and efficacy in multiple studies involving pregnant women when used as an antihypertensive and tocolytic agent. Its role in the treatment of primary dysmenorrhea, bladder instability, and Raynaud's syndrome was also discussed. Its successful use in the management of primary pulmonary hypertension has also been reported.[169] Studies in pregnant women on oral nifedipine have not described significant increases in maternal heart rate.[170] This could be related to the increase in the plasma volume that occurs during the pregnancy and the gradual onset of oral administration.

Uterine blood flow as measured indirectly by Doppler ultrasound has not been shown to be adversely affected by nifedipine.[171,172] Theoretically, nifedipine can adversely affect uterine blood flow by decreasing maternal systemic resistance leading to a fall in maternal blood pressure and a decline in uterine blood flow. Conversely, nifedipine can

positively affect uterine blood flow by relaxing the uterine vascular resistance, which is constricted in hypertensive patients. Mari and colleagues[171] treated 11 mothers with oral short-term nifedipine for preterm labor and did not find any significant difference in the flow velocity waveforms. More long-term therapy with nifedipine was conducted by Moretti and coworkers,[172] who treated 20 patients with preeclampsia ranging from 26 to 35 weeks gestation. Although they found a significant decrease in both maternal systolic and diastolic blood pressures, there was no significant change between the pre- and postnifedipine Doppler studies in either fetal or uteroplacental vessels. Lindow and coinvestigators[173] measured uteroplacental flow in a placebo-controlled study involving a hypertensive gravida by measuring increased radioactivity with a gamma camera after intravenous injection of indium 113m and found no significant change in the blood flow index.

Transplacental passage of nifedipine varies from 0% to 90% with a mean of approximately 66%. Prevost and colleagues[174] detected nifedipine in samples of fetal cord blood and amniotic fluid at concentrations approximately 93% and 53% those of simultaneous maternal vein samples, respectively. Manninen and Juhakoski[175] treated 11 hypertensive patients with 10 mg oral nifedipine 3 times daily. At steady state, maternal nifedipine concentration was 4.3 μg/L. During delivery, they found drug levels in maternal and umbilical sera and in amniotic fluid to be 12.4, 8.6, and 2.5 μg/L, respectively. Small amounts of nifedipine were also found in neonatal urine, indicating that the fetus was able to metabolize the drug. The nifedipine concentration in breast milk on the third day postdelivery was 4.1 μg/L. Nifedipine does not appear to be a teratogenic agent for the fetus.[112] Ferguson and collaborators[176] treated 13 women in preterm labor with oral nifedipine. At delivery, neonatal nifedipine levels were not detectable in 6 of the 11 neonates available for the study; in the remaining 5, values ranged from 29.5 to 1.8 μg/L.

Numerous studies have reported on the positive maternal, fetal, and neonatal outcome for mothers on chronic nifedipine therapy.[177–180] Fenakel and colleagues[177] conducted a randomized trial in which 49 patients with severe preeclampsia between 26 and 36 weeks of gestation were randomly divided into 2 treatment groups receiving either oral nifedipine or hydralazine. They found a statistically significant improvement of blood pressure control for the nifedipine group. Infants born to the nifedipine group also had fewer, mainly minor, complications and spent fewer days in the neonatal intensive-care unit. Bracero and coinvestigators[178] conducted a randomized, prospective study to compare the effectiveness of nifedipine to the tocolytic agent ritodrine in 42 pregnant patients with preterm labor. They found that although nifedipine did delay labor longer than ritodrine, the difference was not statistically significant. However, the nifedipine group had fewer associated maternal and fetal complications described. In a prospective, randomized trial of 66 pregnant patients, Ferguson and collaborators[179] compared nifedipine versus ritodrine with regard to maternal and neonatal outcome. They found nifedipine to be as effective as ritodrine in delaying labor but maternal side effects to be more serious and common in the ritodrine group. Fetal and neonatal outcome were similar for both the nifedipine and ritodrine groups. Similarly, Kupferminc and colleagues[180] found nifedipine to be as effective as ritodrine as a tocolytic agent in their prospective, randomized study involving 71 pregnant women in preterm labor. They observed fewer maternal side effects and similar neonatal outcome for the nifedipine group compared with the ritodrine group. With respect to neonatal outcome, nifedipine is more effective than β-agonists for tocolysis and should be used as a first-line tocolytic agent.[181] The use of nifedipine concurrently with magnesium sulfate should be cautiously done because severe hypotension, neuromuscular blockade, and cardiac depression are possible side effects associated with this combination.[182]

Excretion of nifedipine into breast milk has been documented. Manninen and Juhakoski[175] found relatively high drug concentration in breast milk, indicating that nifedipine was able to diffuse freely into milk. This is probably the result of its lipophilic properties. The Committee on Drugs of the American Academy of Pediatrics considers the use of nifedipine compatible with breast feeding.[42a]

Nicardipine

Nicardipine, another dihydropyridine calcium antagonist, is used for the treatment of angina and hypertension. Similar to nifedipine, it is also used as a tocolytic agent. However, compared with nifedipine, nicardipine is a more potent tocolytic agent but the onset of action is slower.[183]

Forty pregnant women were treated with 20 mg oral nicardipine 3 times a day for mild to moderate hypertension.[184] Treatments were started at approximately 28 weeks for the women and ended on the seventh day postpartum. Low placental passage was observed in 7 women but no accumulation of the drug was detected in the fetus. No perinatal deaths, fetal adverse effects, or adverse neonatal outcomes were observed. Umbilical and cerebral Doppler velocimetry remained stable throughout the course of treatment.

A randomized study compared the efficacy and safety of metoprolol with that of nicardipine in 100 pregnant women with mild to moderate gestational or chronic hypertension.[185] There was no significant difference in the incidence of premature labor, mean gestational age at delivery, or reported side effects. Both had significant reduction in blood pressure, but nicardipine lowered blood pressure more than metoprolol. There was a significant increase in plasma creatinine on metoprolol but not on nicardipine. Umbilical artery resistance

was lower in the nicardipine-treated patients and so was the incidence of cesarean deliveries for fetal distress. There was no significant difference in birth weights and placental weights.

The manufacturer states that a significant amount of nicardipine appears in the milk of lactating rats (Cardene, Roche Labs, product info, 1997). No studies have been reported on the use of nicardipine during human lactation.

OTHER ANTIARRHYTHMIC DRUGS

Adenosine

Adenosine is a purine nucleoside that is effective in treating paroxysmal supraventricular tachycardias (Table 3).[40] Being a natural compound and having a very short half-life of only 7 seconds makes it an attractive drug to use during pregnancy. Podolsky and Varon[186] reported on a 40-year-old in her 39th week of pregnancy experiencing recurrent narrow-complex SVT accompanied by hypotension. An initial 6-mg bolus of adenosine failed to convert, but a second 12-mg dose cardioverted the mother to sinus rhythm within 15 seconds. A healthy infant was born 2 weeks later. Mason et al.[187] reported on a case of a 34-year-old at her 30th week of gestation with paroxysmal SVT. A single 6-mg bolus cardioverted her to sinus rhythm. No change in fetal heart rate was observed and a normal infant was delivered vaginally at term. Chakhtoura and colleagues[188] reported on 4 pregnant patients who presented with SVTs. All were cardioverted with an initial dose of 6 mg of adenosine followed by 2 12-mg doses. One patient was treated successfully twice, at weeks 15 and 24 of gestation. No complications were noted in the mothers or the fetuses at the time of treatment. Five- and 10-minute Apgar scores were all greater than 7. Follow up of both the mother and the offspring at 1 month and 5 years postpartum showed no contributory deleterious effects.

Although the data regarding adenosine's use in pregnancy is limited, this drug looks promising because it is natural and short-acting. The case reports describing its use in pregnancy thus far have been positive, showing both efficacy and a lack of any direct adverse or teratogenic side effects on the fetus.[189] It is unknown if adenosine is excreted in breast milk. However, because of its short half-life, it is assumed that passage of adenosine into breast milk is unlikely.

TABLE 3. Management of Reentrant Supraventricular Tachycardia With Adenosine in Pregnant Patients

Vagal Maneuvers	
No effect	Terminates
↓	↓
Adenosine 6 mg	No additional therapy
↓	
No effect	
↓	
Adenosine 12 mg	
↓	
No effect or hemodynamic instability	
↓	
Sedate cardiovert	
100 J	
200 J	
360 J	
360 J	

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REFERENCES

1. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. *Clin Pharmacokinet*. 1997;33: 328–343.
2. Parbhoo SP, Johnston ID. Effects of oestrogens and progestogens on gastric secretion in patients with duodenal ulcer. *Gut*. 1966;7:612–618.
3. Parker WA. Effects of pregnancy on pharmacokinetics. In: Benet LZ, ed. *Pharmacokinetic Basis for Drug Treatment*. New York: Raven Press; 1984.
4. Widerhorn J, Rubin JN, Frishman WH, et al. Cardiovascular drugs in pregnancy. *Cardiol Clin*. 1987;5:651–674.
5. Krauer B, Krauer F, Hytten F. Drug prescribing in pregnancy. In: Lind T, ed. *Current Reviews in Obstetrics and Gynecology*. Edinburgh: Churchill Livingstone; 1984.
6. Burrow GN, Duffy TP, Kersey R, eds. *Medical Complications During Pregnancy,* 5th ed. Philadelphia: WB Saunders; 1999.
7. Metcalfe J, McAnulty JH, Ueland K. *Burwell and Metcalfe's Heart Disease and Pregnancy: Physiology and Management,* 2nd ed. Boston: Little, Brown; 1986:11–54.
8. Cole PL, Sutton MS. Normal cardiopulmonary adjustments to pregnancy: cardiovascular evaluation. *Cardiovasc Clin*. 1989;19:37–56.
9. Herngren L, Ehrnebo M, Boreus LO. Drug binding to plasma proteins during human pregnancy and in the perinatal period. Studies on cloxacillin and alprenolol. *Dev Pharmacol Ther*. 1983;6:110–124.
10. Wood M, Wood AJ. Changes in plasma drug binding and α1-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther*. 1981;29:522–526.
11. Ralston DH. Perinatal pharmacology. In: Snider SM, Levinson G, eds. *Anesthesia for Obstetrics*. Baltimore: Williams & Wilkins; 1987:50–58.
12. Rotmensch HH, Elkayam U, Frishman W. Antiarrhythmic drug therapy during pregnancy. *Ann Intern Med*. 1983;98:487–497.
13. Elkayam U, Gleicher N. Hemodynamics and cardiac function during normal pregnancy and the puerperium. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy,* 3rd ed. New York: Wiley-Liss; 1998:3–19.
14. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. *Br J Obstet Gynaecol*. 1981;88:1–9.
15. Wadelius M, Darj E, Frenne G, et al. Induction of CYP2D6 in pregnancy. *Clin Pharmacol Ther*. 1997;62:400–407.
16. Levy G. Pharmacokinetics of fetal and neonatal exposure to drugs. *Obstet Gynecol*. 1981;58(suppl 5):9S–16S.
17. Howard FM, Hill JM. Drugs in pregnancy. *Obstet Gynecol Surv*. 1979;34:643–653.
18. Stern L. In vivo assessment of the teratogenic potential of drugs in humans. *Obstet Gynecol*. 1981;58(suppl 5):3S–8S.

19. Berlin CM Jr. Pharmacologic considerations of drug use in the lactating mother. *Obstet Gynecol*. 1981;58(suppl 5):17S–23S.
20. Schanker LS. Passage of drugs across body membranes. *Pharmacol Gynecol*. 1962;14:501–530.
21. Anderson PO. Drugs and breast feeding. In: Knoben JE, Anderson PO, eds. *Handbook of Clinical Drug Data,* 6th ed. Hamilton, IL: Drug Intelligence; 1988:157–184.
22. Okita GT, Gordon RB, Geiling EML. Placental transfer of radioactive digitoxin in rats and guinea pigs. *Proc Soc Exp Biol Med*. 1952;80: 536–538.
23. Saarikoski S. Placental transmission and foetal distribution of 3H-ouabain. *Acta Pharmacol Toxicol*. 1980;46:272–282.
24. Rogers MC, Willerson JT, Goldblatt A, et al. Serum digoxin concentrations in the human fetus, neonate and infant. *N Engl J Med*. 1972;287:1010–1013.
25. Sherman JL, Locke RV. Transplacental neonatal digitalis intoxication. *Am J Cardiol*. 1960;6:834–837.
26. Potondi A. Congenital rhabdomyoma of the heart and intrauterine digitalis poisoning. *J Forensic Sci*. 1967;11:81–88.
27. Whitsett JA, Wallick ET. [3H] ouabain binding and Na+, K+-ATPase activity in human placenta. *Am J Physiol*. 1980;238:E38–E45.
28. Weaver JB, Pearson JF. Influence of digitalis on time of onset and duration of labour in women with cardiac disease. *BMJ*. 1973;3:519–520.
29. Steinberg I, Mitani GM, Harrrison EC, et al. Digitalis glycosides in pregnancy. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy,* 3rd ed. New York: Wiley-Liss, Inc; 1998:426–431.
30. Gewitz M, Woolf P, Frishman WH, et al. Pediatric cardiovascular pharmacology. In: Frishman WH, Sonnenblick EH, Sica DA, eds. *Cardiovascular Pharmacotherapeutics,* 2nd ed. New York: McGraw Hill; 2003:893–918.
31. Copel JA, Friedman AH, Kleinman CS. Management of fetal cardiac arrhythmias. *Obstet Gynecol Clin North Am*. 1997;24:201–211.
32. Ito S, Magee L, Smallhorn J. Drug therapy for fetal arrhythmias. *Clin Perinatol*. 1994;21:543–572.
33. Belhassen B, Pauzner D, Blieden D, et al. Intrauterine and postnatal atrial fibrillation in the Wolff-Parkinson-White syndrome. *Circulation*. 1982;66:1124–1128.
34. Loughnan PM. Digoxin excretion in human breast milk. *J Pediatr*. 1978;92:1019–1020.
35. Anderson JL, Harrison DC, Meffin PJ, et al. Antiarrhythmic drugs: clinical pharmacology and therapeutic uses. *Drugs*. 1978;15:271–309.
36. Spinnato JA, Shaver DC, Flinn GS, et al. Fetal supraventricular tachycardia in utero therapy with digoxin and quinidine. *Obstet Gynecol*. 1984;64:730–735.
37. Johnson WH, Dunnigan A, Fehr P, et al. Association of atrial flutter with orthodromic reciprocating fetal tachycardia. *Am J Cardiol*. 1987; 59:374–375.
38. Whelan AJ. Pregnancy and medical therapeutics. In: McKenzie CR, Ewald GA, eds. *Manual of Medical Therapeutics,* 28th ed. Boston: Little, Brown; 1995:15
39. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol*. 1979;54:366–368.
40. Shotan A, Hurst A, Widerhorn J, et al. Antiarrhythmic drugs during pregnancy and lactation. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy,* 3rd ed. New York: Wiley-Liss, Inc; 1998:373
41. Rosa F. Personal communication. FDA: 1993. In: Briggs GG, Freeman RK, Yaffe SJ, eds. *Drugs in Pregnancy and Lactation. A Reference Guide to Fetal and Neonatal Risk,* 4th ed. Baltimore: Williams & Wilkins; 1994:284,693,759.
42. Roden DM. Antiarrhythmic drugs. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw Hill; 2001:933–970.

42a. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics*. 1994;93: 137–150.

43. Dumesic DA, Silverman NH, Tobias S, et al. Transplacental cardioversion of fetal supraventricular tachycardia with procainamide. *N Engl J Med*. 1982;307:1128–1131.
44. Given BD, Phillippe M, Sanders SP, et al. Procainamide cardioversion of fetal supraventricular tachyarrhythmia. *Am J Cardiol*. 1984;53: 1460–1461.
45. Battiste CE, Neff TW, Evans JF, et al. In utero conversion of supraventricular tachycardia with digoxin and procainamide at 17 weeks' gestation. *Am J Perinatol*. 1992;9:302–303.
46. Pittard WB III, Glazier H. Procainamide excretion in human milk. *J Pediatr*. 1983;102:631–633.
47. Wilson JT, Brown RD, Cherek DR, et al. Drug excretion in human breast milk: principles, pharmacokinetics, and projected consequences. *Clin Pharmacokinet*. 1980;5:1–66.
48. Luoma PV, Kujala PA, Juustila HJ, et al. Efficacy of intravenous disopyramide in the termination of supraventricular arrhythmias. *J Clin Pharmacol*. 1978;18:293–301.
49. Shaxted EJ, Milton PJ. Disopyramide in pregnancy: a case report. *Curr Med Res Opin*. 1979;6:70–72.
50. Leonard RF, Braun TE, Levy AM. Initiation of uterine contractions by disopyramide during pregnancy. *N Engl J Med*. 1978;299:84–85.
51. Tadmor OP, Keren A, Rosenak D, et al. The effect of disopyramide on uterine contractions during pregnancy. *Am J Obstet Gynecol*. 1990; 162:482–486.
52. Abbi M, Kriplani A, Singh B. Preterm labor and accidental hemorrhage after disopyramide therapy in pregnancy. A case report. *J Reprod Med*. 1999;44:653–655.
53. Echizen H, Nakura M, Saotome T, et al. Plasma protein binding of disopyramide in pregnant and postpartum women, and in neonates and their mothers. *Br J Clin Pharmacol*. 1990;29:423–430.
54. Ellsworth AJ, Horn JR, Raisys VA, et al. Disopyramide and N-monodesalkyl-disopyramide in serum and breast milk. *Drug Intell Clin Pharm*. 1989;23:56–57.
55. Barnett DB, Hudson SA, McBurney A. Disopyramide and its N-monodesalkyl metabolite in breast milk. *Br J Clin Pharmacol*. 1982; 14:310–312.
56. Biehl D, Shnider SM, Levinson G, et al. Placental transfer of lidocaine: effects of fetal acidosis. *Anesthesiology*. 1978;48:409–412.
57. Juneja MM, Ackerman WE, Kaczorowski DM, et al. Continuous epidural lidocaine infusion in the parturient with paroxysmal ventricular tachycardia. *Anesthesiology*. 1989;71:305–308.
58. Tucker GT, Boyes RN, Bridenbaugh PO, et al. Binding of anilide-type local anesthetics in human plasma. II. Implications in vivo, with special reference to transplacental distribution. *Anesthesiology*. 1970;33:304–314.
59. Shnider SM, Way EL. Plasma levels of lidocaine (Xylocaine) in mother and newborn following obstetrical conduction anesthesia: clinical applications. *Anesthesiology*. 1968;29:951–958.
60. Brown WU, Bell GC, Lurie AO, et al. Newborn blood levels of lidocaine and mepivacaine in the first postnatal day following maternal epidural anesthesia. *Anesthesiology*. 1975;42:698–707.
61. Shnider SM, Way EL. The kinetics of transfer of lidocaine (Xylocaine) across the human placenta. *Anesthesiology*. 1968;29:944–950.
62. Kuhnert BR, Knapp DR, Kuhnert PM, et al. Maternal, fetal, and neonatal metabolism of lidocaine. *Clin Pharmacol Ther*. 1979;26:213–220.
63. Kim WY, Pomerance JJ, Miller AA. Lidocaine intoxication in a newborn following local anesthesia for episiotomy. *Pediatrics*. 1979; 64:643–645.
64. De Praeter C, Vanhaesebrouck P, De Praeter N, et al. Episiotomy and neonatal lidocaine intoxication. *Eur J Pediatr*. 1991;150:685–686.
65. Brown WU Jr, Bell GC, Alper MH. Acidosis, local anesthetics, and the newborn. *Obstet Gynecol*. 1976;48:27–30.
66. Burney RG, DiFazio CA, Foster JA. Effects of pH on protein binding of lidocaine. *Anesth Analg*. 1978;57:478–480.
67. Kileff MB, James FM III, Dewan D, et al. Neonatal neuro-behavioral responses after epidural anesthesia for cesarean section with lidocaine and bupivacaine. *Anesthesiology*. 1983;57:A403.
68. Scanlon JW, Ostheimer GW, Lurie AO, et al. Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology*. 1976;45:400–405.
69. Campbell RW. Mexiletine. *N Engl J Med*. 1987;316:29–34.
70. Timmis AD, Jackson G, Holt DW. Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet*. 1980;2:647–648.

71. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol*. 1987;157:446–447.
72. Gregg AR, Tomich PG. Mexiletine use in pregnancy. *J Perinatol*. 1988;8:33–35.
73. Currie P, Ramsdale DR. Paranoid psychosis induced by tocainide. *BMJ*. 1984;288:606–607.
74. Holmes B, Brogden RN, Heel RC, et al. Tocainide: a review of its pharmacological properties and therapeutic efficacy. *Drugs*. 1983;26: 93–123.
75. Roden DM, Woosley RL. Tocainide. *N Engl J Med*. 1986;315:41–45.
76. *Drug Information for the Health Care Professional,* vols 1A & 1B (12th ed). Rockville, MD: United States Pharmacopeial Convention; 1992.
77. Doig JC, McComb JM, Reid DS. Incessant atrial tachycardia accelerated by pregnancy. *Br Heart J*. 1992;67:266–268.
78. Wagner X, Jouglard J, Moulin M, et al. Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J*. 1990;119:700–702.
79. Wren C, Hunter S. Maternal administration of flecainide to terminate and suppress fetal tachycardia. *BMJ*. 1988;296:249.
80. Allan LD, Chita SK, Sharland GK, et al. Flecainide in the treatment of fetal tachycardias. *Br Heart J*. 1991;65:46–48.
81. Perry JC, Ayres NA, Carpenter RJ Jr. Fetal supraventricular tachycardia treated with flecainide acetate. *J Pediatr*. 1991;118:303–305.
82. Vautier-Rit S, Dufour P, Vaksmann G, et al. Fetal arrhythmias: diagnosis, prognosis, treatment; apropos of 33 cases. *Gynecol Obstet Fertil*. 2000;28:729–737.
83. Joglar JA, Page RL. Treatment of cardiac arrhythmias during pregnancy: safety considerations. *Drug Saf*. 1999;20:85–94.
84. Macphail S, Walkinshaw SA. Fetal supraventricular tachycardia: detection by routine auscultation and successful in-utero management. Case report. *Br J Obstet Gynaecol*. 1988;95:1073–1076.
85. Brunozzi LT, Meniconi L, Chiocchi P, et al. Propafenone in the treatment of chronic ventricular arrhythmias in a pregnant patient. *Br J Clin Pharmacol*. 1988;26:489–490.
86. Libardoni M, Piovan D, Busato E, et al. Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk. *Br J Clin Pharmacol*. 1991;32:527–528.
87. Frishman WH. Alpha- and beta-adrenergic blocking drugs. In: Frishman WH, Sonnenblick EH, Sica DA, eds. *Cardiovascular Pharmacotherapeutics,* 2nd ed. New York: McGraw Hill; 2003:67–97.
88. Eliahou HE, Silverberg DS, Reisin E, et al. Propranolol for the treatment of hypertension in pregnancy. *Br J Obstet Gynaecol*. 1978; 85:431–436.
89. Sandstrom B. Adrenergic beta-receptor blockers in hypertension of pregnancy. *Clin Exp Hypertens*. 1982;B1:127–141.
90. Rashba EJ, Zareba W, Moss AJ, et al. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. *Circulation*. 1998;97:451–456.
91. Sherif IH, Oyan WT, Bosairi S, et al. Treatment of hyperthyroidism in pregnancy. *Acta Obstet Gynecol Scand*. 1991;70:461–463.
92. Turner GM, Oakley CM, Dixon HG. Management of pregnancy complicated by hypertrophic obstructive cardiomyopathy. *BMJ*. 1968;4: 281–284.
93. Teuscher A, Bossi E, Imhof P, et al. Effect of propranolol on fetal tachycardia in diabetic pregnancy. *Am J Cardiol*. 1978;42:304–307.
94. Bott-Kanner G, Schweitzer A, Reisner SH, et al. Propranolol and hydralazine in the management of essential hypertension in pregnancy. *Br J Obstet Gynaecol*. 1980;87:110–114.
95. Ngo A, Frishman WH, Elkayam U. Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics*. New York: McGraw Hill; 1997:1309–1346.
96. O'Hare MF, Kinney CD, Murnaghan GA, et al. Pharmacokinetics of propranolol during pregnancy. *Eur J Clin Pharmacol*. 1987;27:583–587.
97. Livingstone I, Craswell PW, Bevan EB, et al. Propranolol in pregnancy: three year prospective study. *Clin Exp Hypertens*. 1983;2:341–350.
98. Taylor EA, Turner P. Antihypertensive therapy with propranolol during pregnancy and lactation. *Postgrad Med J*. 1981;57:427–430.
99. Gladstone GR, Hordof A, Gersony WM. Propranolol administration during pregnancy: effects on the fetus. *J Pediatr*. 1975;86:962–964.
100. Tunstall MB. The effect of propranolol on the onset of breathing at birth. *Br J Anaesth*. 1969;41:792.
101. Pruyn SC, Phelan JP, Buchanan GC. Long-term propranolol therapy in pregnancy: maternal and fetal outcome. *Am J Obstet Gynecol*. 1979; 135:485–489.
102. Blake S, MacDonald D. The prevention of the maternal manifestations of pre-eclampsia by intensive antihypertensive treatment. *Br J Obstet Gynaecol*. 1991;98:244–248.
103. Smith MT, Livingstone I, Hooper WD, et al. Propranolol, propranolol glucuronide, and naphthoxylactic acid in breast milk and plasma. *Ther Drug Monit*. 1983;5:87–93.
104. Oakes GK, Walker AM, Ehrenkranz RA, et al. Effects of propranolol infusion on the umbilical and uterine circulations of pregnant sheep. *Am J Obstet Gynecol*. 1976;126:1038–1042.
105. Oakley GD, McGarry K, Limb DG, et al. Management of pregnancy in patients with hypertrophic cardiomyopathy. *BMJ*. 1979;1:1749–1750.
106. Cottrill CM, McAllister RG Jr, Gettes L, et al. Propranolol therapy during pregnancy, labor and delivery: evidence for transplacental drug transfer and impaired neonatal drug disposition. *J Pediatr*. 1977;91: 812–814.
107. Karlberg B, Lundberg D, Aberg H. Excretion of propanolol in human breast milk. *Acta Pharmacol Toxicol*. 1974;34:222–224.
108. Bauer JH, Pape B, Zajicek J, et al. Propranolol in human plasma and breast milk. *Am J Cardiol*. 1979;43:860–862.
109. Hurst AK, Hoffman K, Frishman WH. The use of β-adrenergic blocking agents in pregnancy and lactation. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy,* 3rd ed. New York: Wiley-Liss, Inc; 1998:357–369.
110. Fox RE, Marx C, Stark AR. Neonatal effects of maternal nadolol therapy. *Am J Obstet Gynecol*. 1985;152:1045–1046.
111. Devlin RG, Duchin KL, Fleiss PM. Nadolol in human serum and breast milk. *Br J Clin Pharmacol*. 1981;12:393–396.
112. Briggs GG, Freeman RK, Yaffe SJ, eds. *Drugs in Pregnancy and Lactation. A Reference Guide to Fetal and Neonatal Risk,* 5th ed. Baltimore: Williams & Wilkins; 1998:765.
113. Rasanen J, Jouppila P. Uterine and fetal hemodynamics and fetal cardiac function after atenolol and pindolol infusion. A randomized study. *Eur J Obstet Gynecol Reprod Biol*. 1995;62:195–201.
114. Ellenbogen A, Jaschevatzky O, Davidson A, et al. Management of pregnancy-induced hypertension with pindolol-comparative study with methyldopa. *Int J Gynaecol Obstet*. 1986;24:3–7.
115. Dubois D, Petitcolas J, Temperville B, et al. Treatment of hypertension in pregnancy with β-adrenoceptor antagonist. *Br J Clin Pharmacol*. 1982;13(suppl 2):375S–378S.
116. Schrefer J, Nissen D, et al, eds. *Mosby's GenRx,* 11th ed. St. Louis: Mosby, Inc; 2001.
117. Lindeberg S, Sandstrom B, Lundborg P, et al. Disposition of the adrenergic blocker metoprolol in the late pregnant woman, the amniotic fluid, the cord blood, and the neonate. *Acta Obstet Gynecol Scand*. 1984;118(suppl):61–64.
118. Hogstedt S, Lindberd B, Peng DR, et al. Pregnancy-induced increase in metoprolol metabolism. *Clin Pharmacol Ther*. 1985;37:688–692.
119. Frigo P, Eppel W, Frank A, et al. Management of supraventricular tachycardia during hexoprenaline therapy for preterm labour: benefit of cardioselective beta blockade? *Gynecol Obstet Invest*. 1995;39:212–214.
120. Kaaja R, Hiilesmaa V, Holma K, et al. Maternal anti-hypertensive therapy with beta-blockers associated with poor outcome in very low-birth weight infants. *Int J Gynaecol Obstet*. 1992;38:195–199.
121. Rubin PC, Butters L, Low RA, et al. Atenolol in the treatment of essential hypertension during pregnancy. *Br J Clin Pharmacol*. 1982; 14:279–281.
122. Reynolds B, Butters L, Evans J, et al. First year of life after the use of atenolol in pregnancy associated hypertension. *Arch Dis Child*. 1984; 59:1061–1063.
123. Lydakis C, Lip GY, Beevers M, et al. Atenolol and fetal growth in

pregnancies complicated by hypertension. *Am J Hypertens*. 1999;12: 541–547.
124. Satge D, Sasco AJ, Col JY, et al. Antenatal exposure to atenolol and retroperitoneal fibromatosis. *Reprod Toxicol*. 1997;11:539–541.
125. Hurst A, Shotan A, Hoffman K, et al. Pharmacokinetic and pharmacodynamic evaluation of atenolol during and after pregnancy. *Pharmacotherapy*. 1998;18:840–846.
126. Easterling TR, Brateng D, Schmucker B, et al. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before onset of hypertension. *Obstet Gynecol*. 1999;93:725–733.
127. von Dadelszen P, Ornstein MP, Bull SB, et al. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet*. 2000;355:87–92.
128. Williams E, Morrissey J. A comparison of acebutolol with methyldopa in hypertensive pregnancy. *Pharmatherapeutica*. 1983;3:487–491.
129. Boutroy MJ, Bianchetti G, Dubruc C, et al. To nurse when receiving acebutolol: is it dangerous for the neonate? *Eur J Clin Pharmacol*. 1986;30:737–739.
130. Gilson GJ, Knieriem KJ, Smith JF, et al. Short-acting beta-adrenergic blockade and the fetus. A case report. *J Reprod Med*. 1992;37:277–279.
131. O'Hare MF, Murnaghan GA, Russell CJ, et al. Sotalol as a hypotensive agent in pregnancy. *Br J Obstet Gynaecol*. 1980;87:814–820.
132. Sonesson SE, Fouron JC, Wesslen-Eriksson E, et al. Foetal supraventricular tachycardia treated with sotalol. *Acta Paediatr*. 1998;87:584–587.
133. Lisowski LA, Verheijen PM, Benatar AA, et al. Atrial flutter in the perinatal age group: diagnosis, management and outcome. *J Am Coll Cardiol*. 2000;35:771–777.
134. Hackett LP, Wojnar-Horton RE, Dusci LJ, et al. Excretion of sotalol in breast milk [Letter]. *Br J Clin Pharmacol* 1990;29:277–278.
135. de Swiet M. Maternal blood pressure and birthweight. *Lancet*. 2000; 355:81–82.
136. McKenna WJ, Harris L, Rowland E, et al. Amiodarone therapy during pregnancy. *Am J Cardiol*. 1983;51:1231–1233.
137. Pitcher D, Leather HM, Storey GCA, et al. Amiodarone in pregnancy. *Lancet*. 1983;1:597–598.
138. Gembruch U, Manz M, Bald R, et al. Repeated intravascular treatment with amiodarone in a fetus with refractory supraventricular tachycardia and hydrops fetalis. *Am Heart J*. 1989;118:1335–1338.
138a. Arnour P, Seyral P, Llurens M, et al. Amiodarone and digoxin for refractory fetal tachycardia. *Am J Cardiol*. 1987;59:166–167.
139. Penn IM, Barrett PA, Pannikote V, et al. Amiodarone in pregnancy. *Am J Cardiol*. 1985;56:196–197.
140. Valensise H, Civitella C, Garzetti GG, et al. Amiodarone treatment in pregnancy for dilatative cardiomyopathy with ventricular malignant extrasystole and normal maternal and neonatal outcome. *Prenat Diagn*. 1992;12:705–708.
140a. Strunge P, Frandsen J, Andreasen F. Amiodarone during pregnancy. *Eur Heart J*. 1988;9:106–109.
141. Robson D, Jeeva RMV, Storey GCA, et al. Use of amiodarone during pregnancy. *Postgrad Med J*. 1985;61:75–77.
142. DeWolf D, DeSchepper J, Verhaaren H, et al. Congenital hypothyroidism goiter and amiodarone. *Acta Paediatr Scand*. 1988;77:616–618.
143. Widerhorn J, Bhandari AK, Bughi S, et al. Fetal and neonatal adverse effects profile of amiodarone treatment during pregnancy. *Am Heart J*. 1991;122:1162–1165.
144. Laurent M, Betremieux P, Biron Y, et al. Neonatal hypothyroidism after treatment by amiodarone during pregnancy. *Am J Cardiol*. 1987;60:142.
145. Magee LA, Downar E, Sermer M, et al. Pregnancy outcome after gestational exposure to amiodarone in Canada. *Am J Obstet Gynecol*. 1995;172:1307–1311.
146. De Catte L, De Wolf D, Smitz J, et al. Fetal hypothyroidism as a complication of amiodarone treatment of persistent fetal supraventricular tachycardia. *Prenat Diagn*. 1994;14:762–765.
147. Matsumura LK, Born D, Kunii IS, et al. Outcome of thyroid function in newborns from mothers treated with amiodarone. *Thyroid*. 1992;2: 279–281.
148. Ovadia M, Brito M, Hoyer GL, et al. Human experience with amiodarone in the embryonic period. *Am J Cardiol*. 1994;73:316–317.
149. Magee L, Nulman I, Rovert JF. Neurodevelopment after in utero amiodarone exposure. *Neurotoxicol Teratol*. 1999;21:261.
150. Bartalena L, Bogazzi F, Braverman LE. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest*. 2001;24:116–130.
151. Grosso S, Berardi R, Cioni M, et al. Transient neonatal hypothyroidism after gestational exposure to amiodarone: a follow-up of two cases. *J Endocrinol Invest*. 1998;21:699–702.
152. Gutgesell M, Overholt E, Boyle R. Oral bretylium tosylate use during pregnancy and subsequent breastfeeding: a case report. *Am J Perinatol*. 1990;7:144–145.
153. Byerly WG, Hartmann A, Foster DE, et al. Verapamil in the treatment of maternal paroxysmal supraventricular tachycardia. *Ann Emerg Med*. 1991;20:552–554.
154. Klein V, Repke JT. Supraventricular tachycardia in pregnancy: cardioversion with verapamil. *Obstet Gynecol* 1984;63(suppl 3):16S–18S.
155. Orlandi C, Marlettini MG, Cassani A, et al. Treatment of hypertension during pregnancy with the calcium antagonist verapamil. *Curr Ther Res*. 1986;39:884–893.
156. Belfort MA, Anthony J, Buccimazza A, et al. Hemodynamic changes associated with intravenous infusion of the calcium antagonist verapamil in the treatment of severe gestational proteinuric hypertension. *Obstet Gynecol*. 1990;75:970–974.
157. Belfort M, Akovic K, Anthony J, et al. The effect of acute volume expansion and vasodilatation with verapamil on uterine and umbilical artery Doppler indices in severe preeclampsia. *J Clin Ultrasound*. 1994;22:317–325.
158. Ulmsten U. Inhibition of myometrial hyperactivity by Ca antagonists. *Dan Med Bull*. 1979;26:125–126.
159. Kanzaki T, Murakami M, Kobayashi H, et al. Hemodynamic changes during cardioversion in utero: a case report of supraventricular tachycardia and atrial flutter. *Fetal Diagn Ther*. 1993;8:37–44.
160. Kleinman CS, Copel JA, Weinstein EM, et al. Treatment of fetal supraventricular tachyarrhythmias. *J Clin Ultrasound*. 1985;13:265–273.
161. Andersen HJ. Excretion of verapamil in human milk. *Eur J Clin Pharmacol*. 1983;25:279–280.
162. Miller MR, Withers R, Bhamra R, et al. Verapamil and breast-feeding. *Eur J Clin Pharmacol*. 1986;30:125–126.
163. Inoue H, Unno N, Ou M-C, et al. Level of verapamil in human milk. *Eur J Clin Pharmacol*. 1984;26:657–658.
164. Holbrook RH Jr, Gibson RN, Voss EM. Tocolytic and cardiovascular effects of the calcium antagonist diltiazem in the near-term pregnant rabbit. *Am J Obstet Gynecol*. 1988;159:591–595.
165. Downing SJ, Edwards D, Hollingsworth M. Diltiazem pharmacokinetics in the rat and relationship between its serum concentration and uterine and cardiovascular effects. *Br J Pharmacol*. 1987;91:735–745.
166. Okada M, Inoue H, Nakamura Y, et al. Excretion of diltiazem in human milk. *N Engl J Med*. 1985;312:992–993.
167. Frishman WH, Sica DA. Calcium channel blockers. In: Frishman WH, Sonnenblick EH, Sica DA, eds. *Cardiovascular Pharmacotherapeutics,* 2nd ed. New York: McGraw Hill; 2003:105–130.
168. Childress CH, Katz VL. Nifedipine and its indications in obstetrics and gynecology. *Obstet Gynecol*. 1994;83:616–624.
169. Nootens M, Rich S. Successful management of labor and delivery in primary pulmonary hypertension. *Am J Cardiol*. 1993;71:1124–1125.
170. Pirhonen JP, Erkkola RU, Ekblad UU, et al. Single dose of nifedipine in normotensive pregnancy: nifedipine concentrations, hemodynamic responses, and uterine and fetal flow velocity waveform. *Obstet Gynecol*. 1990;76:807–811.
171. Mari G, Kirshon B, Moise KJ, et al. Doppler assessment of the fetal and uteroplacental circulation during nifedipine therapy for preterm labor. *Am J Obstet Gynecol*. 1989;161:1514–1518.
172. Moretti NM, Fairlie FM, Akl-S, et al. The effect of nifedipine therapy on fetal and placental Doppler waveforms in preeclampsia remote from term. *Am J Obstet Gynecol*. 1990;163:1844–1848.
173. Lindow SW, Davies N, Davey DA, et al. The effect of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy. *Br J Obstet Gynaecol*. 1988;96:1276–1281.
174. Prevost RR, Akl SA, Whybrew WD, et al. Oral nifedipine pharmacokinetics in pregnancy-induced hypertension. *Pharmacotherapy*. 1992; 12:174–177.
175. Manninen AK, Juhakoski A. Nifedipine concentrations in maternal and

umbilical serum, amniotic fluid, breast milk and urine. *Int J Clin Pharmacol Res*. 1991;11:231–236.
176. Ferguson JE Jr, Schutz T, Pershe R, et al. Nifedipine pharmacokinetics during preterm labor tocolysis. *Am J Obstet Gynecol*. 1989;161:1485–1490.
177. Fenakel K, Fenakel G, Appelman Z, et al. Nifedipine in the treatment of severe preeclampsia. *Obstet Gynecol*. 1991;77:331–337.
178. Bracero LA, Leikin E, Kirschenbaum N, et al. Comparison of nifedipine and ritodrine for the treatment of preterm labor. *Am J Perinatol*. 1991;8:365–369.
179. Ferguson JE Jr, Dyson DC, Schutz T, et al. A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome. *Am J Obstet Gynecol*. 1990;163:105–111.
180. Kupferminc M, Lessing JB, Yaron Y, et al. Nifedipine versus ritodrine for suppression of preterm labor. *Br J Obstet Gynaecol*. 1993;100:1090–1094.
181. Tsatsaris V, Papatsonis D, Goffinet F, et al. Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. *Obstet Gynecol*. 2001;97:840–847.
182. Khedun SM, Maharaj B, Moodley J. Effects of antihypertensive drugs on the unborn child: what is known, and how should this influence prescribing? *Paediatr Drugs*. 2000;2:419–436.
183. Maigaard S, Forman A, Andersson KE, et al. Comparison of the effects of nicardipine and nifedipine on isolated human myometrium. *Gynecol Obstet Invest*. 1983;16:354–366.
184. Carbonne B, Jannet D, Touboul C, et al. Nicardipine treatment of hypertension during pregnancy. *Obstet Gynecol*. 1992;81:908–914.
185. Jannet D, Carbonne B, Sebban E, et al. Nicardipine versus metoprolol in the treatment o f hypertension during pregnancy: a randomized comparative trial. *Obstet Gynecol*. 1994;84:354–359.
186. Podolsky SM, Varon J. Adenosine use during pregnancy. *Ann Emerg Med*. 1991;29:1027–1028.
187. Mason BA, Ricci-Goodman J, Koos BJ. Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. *Obstet Gynecol*. 1992;80:478–480.
188. Chakhtoura N, Angioli R, Yasin S. Use of adenosine for pharmacological cardioversion of SVT in pregnancy. *Prim Care*. 1998;5:154.
189. Leffler S, Johnson DR. Adenosine use in pregnancy: lack of effect on fetal heart rate. *Am J Emerg Med*. 1992;10:548–549.