Cardiovascular Medications in Pregnancy
A Primer

Karen L. Florio, DO[a,b,*], Christopher DeZorzi, MD[b,c], Emily Williams, MD[b], Kathleen Swearingen, MSN, APRN, FNP-C[a], Anthony Magalski, MD, FHFSA[b,c]

KEYWORDS

• Cardio-obstetrics • Cardiac medications • Pregnancy • Medication safety
• Heart disease in pregnancy

KEY POINTS

- Pregnancy induces dramatic physiologic and anatomic changes in the cardiovascular system beginning in the first trimester and continuing through the postpartum period.
- Maternal cardiac arrhythmias during pregnancy are a common occurrence and treatment should be considered from both obstetric and electrophysiologic standpoints.
- Anticoagulation and antiplatelet medications are prescribed commonly in both cardiology and obstetrics for various reasons.

INTRODUCTION

Cardiovascular disease and its related disorders are the leading causes of maternal morbidity and mortality in the United States.[1,2] The increasing age at first pregnancy coupled with the rising rates of obesity likely contribute to this trend. More women are desiring delayed fertility, which results in higher rates of hypertensive disorders during gestation.[3] Increases in women with repaired congenital cardiovascular disease becoming pregnant also add to this patient population. As a result, the use of cardiovascular medications during pregnancy also is increasing. It has been reported that up to 94% of women take at least 1 medication while pregnant and approximately 70% are taking medication during fetal organogenesis.[4] The ROPAC trial reported as many as 28% of women with underlying cardiovascular conditions were taking medication, a number that is likely higher in the United States because the burden of disease is significantly greater.[5] As such, clinicians need to have a breadth of fundamental knowledge regarding the safety profiles of medication use during pregnancy. Many different factors need to be balanced when deciding on medications during pregnancy, including gestational age, reported teratogenicity, placental transport, altered pharmacokinetics, route of administration, and dosing. Safety profiles are limited because reports of teratogenic effects are from observational trials or registries due to the ethical dilemma of research on this vulnerable population.[4] The purpose of this review is to guide clinical decisions for both obstetricians and cardiologists when confronted with a pregnant woman affected by cardiovascular disease requiring treatment. This is not meant to be an all-encompassing review of every medication utilized during pregnancy but rather an overview of the more commonly used cardiovascular medications (**Table 1**) from preconception through postpartum and lactation.

[a] Heart Disease in Pregnancy Program, Saint Luke's Hospital of Kansas City, 4401 Wornall Road PEET Center, Kansas City, MO 64111, USA; [b] University of Missouri-Kansas City School of Medicine, 4401 Wornall Road PEET Center, Kansas City, MO 64111, USA; [c] Saint Luke's Mid America Heart Institute, Kansas City, MO, USA
* Corresponding author. Heart Disease in Pregnancy Program, Saint Luke's Hospital of Kansas City, 4401 Wornall Road PEET Center, Kansas City, MO 64111.
E-mail address: kflorio@saint-lukes.org

Cardiol Clin 39 (2021) 33–54
https://doi.org/10.1016/j.ccl.2020.09.011

Table 1
Classification of cardiac medications used during pregnancy

Drug	Mechanism of Action	Onset of Action	Metabolism	Side Effects	Teratogenicity	Lactation/ Breastfeeding
Abciximab	Monoclonal antibody, binds to glycoprotein IIb/IIIa, inhibits platelet aggregation	Half-life: 30 min Onset: 10 min	Opsonization by way of reticuloendothelial system (when bound to platelets)	Bleeding, chest pain, hypotension, nausea, vomiting, abdominal pain, thrombocytopenia, anaphylaxis	No mutagenicity in animal models; limited human data without evidence of teratogenicity; crosses placenta	No reports of use in literature; unlikely crosses into breast milk (large molecule)
Acebutolol	Cardioselective β_1-blockade	Half-life: 3–4 h	Extensive first-pass metabolism	Bronchospasm, bradycardia, heart block, fatigue, dizziness, diarrhea, nausea, vomiting	No increased teratogenicity, some reports of neonatal hypotension	AAP recommends giving "with caution." plasma ratio in milk higher than other β-blockers
Adenosine	Slows AV node conduction, activation of cell-surface A_1 and A_2 adenosine receptors	Half-life: 10 s	Phosphorylation intracellularly to adenosine monophosphate	Flushing, dyspnea, chest discomfort, headaches, nausea	No reported teratogenicity (rapid degradation by placenta); no effect on fetal heart rate	Paucity of data—likely safe due to short half life
Alteplase	Binds to fibrin and converts plasminogen to plasmin	Half-life: initial 5 min with terminal half-life of 72 min	Hepatic metabolism	Hemorrhage, angioedema, anaphylaxis, fever	No mutagenicity in animal models (minimal placental passage)	No data available
Amiloride	Potassium-sparing diuretic, inhibits sodium absorption in the renal tubules	Half-life: 6–9 h	Excreted unchanged in kidneys	Headache, weakness, nausea, vomiting, muscle cramps, hyperkalemia, aplastic anemia, neutropenia	No mutagenicity in animal models. Limited human data (1 case report with skeletal anomalies)	No data available

Amiodarone	Benzofuran derivative; relaxes vascular smooth muscle; acts as an antiarrhythmic (prolongs QRS and QT intervals)	Half-life: depends on patient but varies from 15–142 d (active metabolite 14–75 d) Plasma half-life 3.2–79.7 h.	CYP34 A and CYP2C8 in liver	Nausea, vomiting, visual disturbances, hypothyroidism, skin discoloration, AV block, QT prolongation	Fetal goiter, fetal thyroid dysfunction, possible association with IUGR, congenital heart defects, neurodevelopmental delay; crosses term placenta in higher concentration than maternal serum	Avoid use during breastfeeding
Amlodipine	Calcium channel blocker: blocks calcium entry into cells causing smooth muscle relaxation	Half-life: 30–50 h	90% metabolized in liver, 10% excreted unchanged in urine	Peripheral edema, fatigue, palpitations, flushing, nausea, hypotension	No mutagenicity in animal models; limited human data but small case series with increased fetal loss and limb defects	Limited data—probably compatible
Argatroban	Inhibits thrombin-catalyzed or induced reactions; activates factors V, VIII, and XIII; enhances platelet aggregation	39–51 min	Hydroxylation and aromatization in the liver	Chest pain, hypotension, cough, hypersensitivity reaction, fever, ventricular arrhythmias, bleeding, bradycardia	Minimal animal data (no teratogenic effects at dose 0.3× human doses); minimal human data available (likely maternal benefit outweighs fetal toxicity)	No data available
Aspirin	Blocks prostaglandin synthesis (nonselective COX-1 and COX-2 inhibitor)	13–19 min	Hydrolyzed in plasma to salicylic acid, metabolized in liver	Bleeding, dyspepsia, vomiting, thrombocytopenia, nausea	At large doses, teratogenic to animal models; no increased risk of human teratogenesis with normal dosing	WHO Working Group on Human Lactation classified as unsafe

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Drug	Mechanism of Action	Onset of Action	Metabolism	Side Effects	Teratogenicity	Lactation/ Breastfeeding
Atenolol	Cardioselective β_1-blockade	6–7 h	Minimal metabolism in liver, most is excreted unchanged in the urine	Bradycardia, hypotension, bronchospasm, diarrhea, fatigue, nausea, SLE-like reaction	Decreased fetal weight in animal models; crosses placenta, not associated with birth defects but with FGR	Excreted in breast milk in higher amounts than maternal plasma, WHO recommends caution with breastfeeding
Carvedilol	Combined α_1/β-adrenergic blocker	7–10 h	Hydroxylated by CYP system in liver; also undergoes glucuronidation; 98% protein bound	Bradycardia, hyperglycemia, nausea, headache, BUN elevation, AST/ALT elevation, pulmonary edema	Animal models with decreased fetal weight and pregnancy loss; no increased teratogenicity but increase neonatal hypoglycemia	Limited human data—probably compatible
Cholestyramine	Forms resin that acts as a bile acid sequestrant and limits absorption of bile	6 min	No modification or absorption in gut, excreted bound to bile acids	Constipation, flatulence, nausea, vomiting, steatorrhea	No mutagenicity in animal models; no fetal teratogenicity but some cases of abnormal fetal heart tracings and meconium	Limited human data—probably compatible
Clonidine	α_2-Adrenergic agonist	6–23 h	Hydroxylation by CYP enzymes in liver (but is poorly understood)	Somnolence, headaches, nightmares, emotional lability, hypotension, reflex HTN with withdrawal	No mutagenicity in therapeutic doses in animal models, increased fetal loss in higher doses in animal models; some case reports of teratogenicity with first trimester use	Excreted in breast milk in higher concentrations than maternal plasma; neonatal hypotension. Likely compatible

Clopidogrel	Platelet inhibitor that binds to $P2Y_{12}$ADP receptors on platelets preventing aggregation	6 h; active metabolite is 30 min	85%–90% metabolized by liver by CYP system	Bleeding, pruritis, agranulocytosis, pancytopenia	No mutagenicity in animal models; limited human data with 1 report of PFO (likely compatible)	Limited data but likely compatible
Dalteparin	Potentiates activity of ATIII, inhibiting factor Xa and thrombin	IV: half-life 2 h Subcutaneous: 3–5 h	Liver and reticuloendothelial system biotransformation (disulphation and depolymerization)	Bleeding, thrombocytopenia, hematuria, ALT/AST elevation, rash, pruritis	No mutagenicity in animal models; no increased teratogenicity in human fetuses	Not transferred in breast milk; compatible
Diltiazem	Calcium channel blocker: blocks calcium entry into cells causing smooth muscle relaxation	Immediate release: 3–4.5 h Delayed-release: 6–9 h	Extensive first-pass metabolism in CYP3A4 system	Headaches, dizziness, hypotension, bradycardia, first-degree AV block, AST/ALT elevations, syncope	Increase in limb and tail malformations in animal models; small increase in fetal loss in first trimester in humans, no increase in birth defects	Limited human data—likely compatible
Digoxin	Hemodynamic, electrophysiologic and neurohormonal effects; stimulates parasympathetic nervous system via vagus nerve, reversibly inhibits sodium-potassium ATPase enzyme	1.5–2 d	Only approximately 13% is metabolized (skeletal muscle), 25% protein bound	Dizziness, headaches, nausea, vomiting, anorexia, bradycardia, palpitations, gynecomastia, depression, AV block, delirium	No mutagenicity in animal models; no increased risk of birth defects when used in first trimester (utilized in pregnancy for fetal SVT)	AAP classifies as compatible with breastfeeding
Enoxaparin	Inhibition of factor Xa, binds to and accelerates ATIII	4.5 h	Desulphation and polymerization in liver; 80% protein bound	Hemorrhage, fever, ALT/AST elevations, nausea, thrombocytopenia, osteoporosis (long-term use)	No mutagenicity in animal models; does not cross human placenta, no increased fetal risks	Compatible

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Drug	Mechanism of Action	Onset of Action	Metabolism	Side Effects	Teratogenicity	Lactation/ Breastfeeding
Enalapril	RAAS activated angiotensin II enzyme inhibitor	11–14 h	Hydrolyzed by de-esterification by hepatic enzymes; <50% protein bound	Dizziness, hypotension, fatigue, cough, hyperkalemia, Cr elevations, photosensitivity, angioedema, neutropenia	No mutagenicity in animal models with doses much higher than used in humans, some studies with fetal wastage and nephrotoxicity; human data suggests outcomes similar to lisinopril	Compatible
Esmolol	Cardioselective β_1-blockade	2 min	Rapid hydrolysis of ester linkage in RBCs; 55% protein bound	Hypotension, nausea, dizziness, somnolence, agitation, headaches, bradycardia	No mutagenicity in animal models; no increased risk of human birth defects but neonatal effects include apnea and hypoglycemia	Limited human data—probably compatible
Ezetimibe	Selectively inhibits absorption of cholesterol and phytosterol (targets Niemann-Pick C1-like protein)	22 h	Rapidly and extensively metabolized by phase II glucuronidation in liver	Upper respiratory infections, diarrhea, myalgias, fatigue, back pain, hypersensitivity, hepatitis	No mutagenicity at therapeutic dosing (associated with skeletal changes at doses 10× human dose) in animal models; no human data	No human data—animal models suggest risk
Flecainide	Blocks fast inward sodium channels, shortens action potential of Purkinje fibers	13 h	Metabolized by CYP2D6 and CYP1A2 in liver	Dizziness, headaches, fatigue, palpitations, chest pain, tremors, abdominal pain, dyspnea, heart block, QT prolongation	In high-dose models, increased clubbed feet and skeletal defects; no increased teratogenicity in humans but in neonates, increased bilirubin and abnormal EKGs	Limited human data—probably compatible

Fondaparinux	ATIII-mediated selective inhibition of factor Xa	17–21 h	Not metabolized, 94% protein bound	Bleeding, AST/ALT elevations, anemia	No mutagenicity in animal models; does not cross placenta (1 case report documenting neonatal exposure), no teratogenicity	No human data—probably compatible
Furosemide	Blocks tubular absorption of sodium and chloride in proximal and distal tubules	4–4.5 h	Kidneys clear 85%, 40% biotransformation in the liver	Hypokalemia, AST/ALT elevation, hyperuricemia, hyperglycemia, hypotension, muscle cramps, weakness, metabolic acidosis, ototoxicity	Skeletal anomalies in animal models in high doses; can cross the human placenta and increase fetal urine production, possible increase in PDA, neonatal sensorineural hearing loss	Limited human data—probably compatible
Gemfibrozil	Activates peroxisome proliferator-activated receptors, which alter lipid metabolism	1.5 h	Hydroxylation at the 5′methyl and 4′ positions in the CYP2C8 enzymatic system	Dyspepsia, abdominal pain, diarrhea, nausea, vomiting, AST/ALT elevations	No mutagenicity in animal models; limited human data, some case reports of brain and facial defects	No human data—potential toxicity
Heparin	Inhibition of factor Xa	1.5 h	Biotransformation in the liver and reticuloendothelial system	Bleeding, thrombocytopenia, prolonged clotting time, fever, AST/ALT elevations, HIT	No mutagenicity in animal models; does not cross human placenta	Compatible
Hydrochlorothiazide	Inhibits sodium and chloride in proximal renal tubules and reduces absorption of water	5.6–14.8 h	Not metabolized	Electrolyte imbalances, hypercalcemia, dizziness, anorexia, muscle cramps	No mutagenicity in animal models; no increase teratogenicity but associated with neonatal thrombocytopenia, bleeding, electrolyte imbalances	Compatible (may decrease milk production in first month)

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Drug	Mechanism of Action	Onset of Action	Metabolism	Side Effects	Teratogenicity	Lactation/ Breastfeeding
Hydralazine	Interferes with calcium transport, also competes with protocollagen prolyl hydroxylase (preventing degradation of HIF-α1)	2.2–7.8 h	Hydroxylation and glucuronidation in liver	Headache, hypotension, palpitations, nausea, vomiting, diarrhea, neutropenia, lupus-like reaction	Abnormal embryo development in animal models likely due to uteroplacental hypoperfusion; no reports of teratogenicity in limited human data	Limited human data—probably compatible
Labetalol	Nonselectively antagonizes β_1/β_2-receptors, α_1-agonist	1.7–.1 h	Metabolized to glucuronide metabolites in liver	Hypotension, dizziness, headaches, fatigue, edema, BUN/Cr elevation, bronchospasm, Raynaud disease, bradycardia, syncope	No mutagenicity in animal models but decreased birth weights; some reports associated with hypospadias, low birth weight	Limited human data—probably compatible
Lisinopril	Angiotensin II enzyme inhibitor	12.6 h	Excreted unchanged in the urine; no protein binding	Dizziness, hypotension, Cr elevations, cough, fatigue, photosensitivity, angioedema, neutropenia	Abnormal/birth defects in animal models; human data in first trimester limited to conclude teratogenicity but does increased risk of malformations and death in second/third trimester	Not compatible
Methy-ldopa	Stimulates central inhibitory α-adrenergic receptors	105 min	Extensively metabolized in the liver	Sedation, angina, weakness, bradycardia, diarrhea, vomiting, myocarditis, hypotension	No mutagenicity in animal models; single study in humans showing malformations	Compatible

Metoprolol	β_1-adrenergic receptor inhibitor	3–7 h	Extensive first pass metabolism through CYP2D6 enzymatic system	Bradycardia, influenza-like symptoms, fatigue, headache, rash, hyperuricemia, sleep disturbances, heart block	No mutagenicity in animal models; some small case studies with fetal malformations, associated with low birth weight	Compatible
Milrinone	Inhibits erythrocyte phosphodiesterase in myocardium and vascular smooth muscle, leading to increased cAMP in red cells	2.3 h	O-glucuronidation in liver, 80% protein bound	Ventricular arrhythmias, ectopy, tachycardia, hypotension, headache, anaphylaxis	No mutagenicity in animal studies; no teratogenicity in human studies	No human data—probably compatible
Nadolol	Nonselective β-adrenergic blocker	20–24 h	Excreted unchanged in the kidney	Bradycardia, fatigue, dizziness, nausea, vomiting, constipation, Raynaud disease, bronchospasm	No mutagenicity in animal studies; no increased risk of teratogenicity but is associated with low birth weight	Compatible
Nicardipine	Calcium channel blocker: blocks calcium entry into cells causing smooth muscle relaxation	8.6 h	Metabolized extensively in liver; 95% protein bound	Headache, dizziness, hypotension, nausea, vomiting, tachycardia, palpitations	May interfere with embryo development in small animal studies; no increased teratogenicity in small studies	Probably compatible
Nifedipine	Inhibits L-type voltage-gated calcium channels	2 h	Metabolized by CYP3A4 enzymatic system in liver; 92%–98% protein bound	Headaches, fatigue, flushing, nausea, vomiting, palpitations, hypotension, bradycardia	May interfere with embryo development in small animal studies; no increased teratogenicity in small studies	Compatible

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Drug	Mechanism of Action	Onset of Action	Metabolism	Side Effects	Teratogenicity	Lactation/ Breastfeeding
Propafenone	Class 1C antiarrhythmic (reduction in upstroke of action potential); reduces fast inward sodium ions	2–10 h	Extensively metabolized in liver; 97% protein bound	Dizziness, nausea, edema, taste changes, vomiting, blurred vision, ecchymosis, ventricular arrhythmias, QT prolongation	Embryotoxic in animals at doses 3–6× maximum human dose; limited human data but appears to have no increased teratogenicity, is associated in small case series with fetal loss	Limited human data—probably compatible
Propranolol	Nonselective β-adrenergic antagonist	8 h	Side chain oxidation (to metabolites) or glucuronidation in liver; 85%–96% protein bound	Fatigue, dizziness, bradycardia, hypotension, nausea, vomiting, purpura, disorientation, depression, heart block	No mutagenicity in animal models; no increased teratogenicity but is associated with decreased birth weights	Compatible
Rivaroxaban	Inhibits factor Xa	5–9 h	Metabolized by CYP enzymatic system in liver; 92%–95% protein bound	Bleeding, back pain, pruritis, dizziness, thrombocytopenia, agranulocytosis	No mutagenicity in animal models; minimal human data with only 1 case report of teratogenicity, does cross placenta and cause neonatal bleeding risk	Limited human data—caution recommended
Spironolactone	Inhibits aldosterone-dependent sodium exchange channels in distal convoluted tubules	1.4 h	Deacetylation and excretion in the urine; >90% protein bound	Electrolyte imbalances, nausea, vomiting, dizziness, lethargy, menstrual irregularities, GI bleeding, gastritis, gynecomastia	Antiandrogenic effect in animal data with adverse effects on male genitalia, this was not seen in human data, some case reports with ambiguous genitalia	Compatible

Sotalol	β_1-adrenergic antagonist, rapid potassium channel inhibitor	10–20 h	Not metabolized and not protein bound	Fatigue, dizziness, bradycardia, palpitations, headaches, insomnia, heart block, QT prolongation	No mutagenicity in animal models but 1 case of fetal death secondary to arrhythmia; no teratogenicity	Considered unsafe (excreted in breast milk in large quantities)
Timolol	β_1/β_2-adrenergic antagonist	2.9 h	Metabolized by P450 2D6 system in liver; 10% protein bound	Bradycardia, fatigue, dizziness, nightmares, headaches, heart block, ocular irritation	No mutagenicity in animal models; no teratogenicity but is associated with low birth weight	Compatible
Verapamil	Calcium channel blocker: blocks calcium entry into cells causing smooth muscle relaxation	2.8–7.4 h	Extensively metabolized by P450 system in liver	Dizziness, nausea, hypotension, headaches, fatigue, hypotension, bradycardia, hepatotoxicity	Possible cardiac and CNS malformations in animal models; some case reports of teratogenicity and is associated with low birth weight	Compatible
Warfarin	VKA	37–89 h	Oxidation in liver by CYP system, limited conjugation	Bleeding, ecchymosis, abdominal pain, lethargy, taste changes, paresthesia, skin necrosis, calciphylaxis	Mutagenicity in animal models; associated with structural malformations in dose-dependent manner in human data, neonatal bleeding	Compatible

Abbreviations: AAP, American Academy of Pediatrics; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATIII, antithrombin III deficiency; AV, atrioventricular; BUN, blood urea nitrogen; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; COX, cyclo-oxygenase; CR, creatinine; CYP, cytochrome P450; GI, gastrointestinal; HIF, hypoxia-inducible factor; HIT, heparin-induced thrombocytopenia; HTN, hypertension; IUGR, intrauterine growth restriction; PDA, patent ductus arteriosus; P2Y12ADP, chemo receptor for adenine diphosphate; PFO, patent foramen ovale; RAAS, renin angiotensin system; RBC, red blood cell; SLE, systemic lupus; WHO, World Health Organization.

PHYSIOLOGIC CHANGES IN PREGNANCY

Cardiovascular Changes

Pregnancy induces dramatic physiologic and anatomic changes in the cardiovascular system beginning in the first trimester and continuing through the postpartum period. These coordinated changes function to supply the growing fetus with oxygen and nutrients throughout pregnancy. Prior to conception, only approximately 2% to 3% of total cardiac output flows through the uterine arteries compared with 25% at term.[6,7] This shift in cardiac output begins very early on, peaking at term, and returning to normal at 3 months to 6 months.[6]

The heart undergoes progressive adaptive remodeling and structural alterations, including displacement into the thoracic cavity that is upward and forward.[8] This creates a barrel shape to the maternal chest, giving the appearance of cardiomegaly on chest imaging and left axis deviation on electrocardiogram (EKG) recordings.[9,10] Left ventricular wall mass and right ventricular wall mass increase, by 52% and 40%, respectively.[11–14] This likely is due to a combination of increased blood volume and signaling from progesterone and vascular endothelial growth factors, leading to hypertrophy of the cardiac myocytes and increased angiogenesis.[15,16] Placental lactogen enhances erythropoietin production, leading to an increase in red blood cell mass by 30%.[17,18] Total body water and plasma volume increase by a larger proportion, creating a physiologic anemia.[19,20] Increased estrogen activates the renin-angiotensin-aldosterone system, increasing sodium resorption and thereby water uptake. Estrogen also mediates the release of vasopressin from the hypothalamus, lowering the maternal osmostat and decreasing the thirst threshold. This leads to a decrease in colloid osmotic pressure, which contributes to dependent edema and an increased risk for pulmonary edema.[21] This physiologic dependent edema can be difficult to discern from edema secondary to cardiac failure.

To accommodate for the increasing volume, there is a compensatory increase in venous and arterial distensibility and a softening of the intimal lining of the arterial vessels.[14,22,23] Nitric oxide, relaxin, and progesterone mediate smooth muscle relaxation and a drop in systemic vascular resistance (SVR).[24,25] This drop in SVR is offset by the increase in preload and subsequently cardiac output, which leads to minimal change in the mean arterial pressure. This 25% to 30% drop in blood pressure reaches it's nadir in mid–second trimester and returns to normal prepregnancy values by the third trimester.[26,27] Dimensions of all cardiac chambers increase to compensate for the continued increase in plasma volume, resulting in trivial regurgitation in the mitral, tricuspid, and pulmonary valves.[28] Cardiac myocyte hypertrophy coupled with increased myocyte stretch leads to higher contractility without an increase in left ventricular strain or a change in overall ejection fraction.[8,13] There is a sharp increase in cardiac output in the first trimester and again in the third trimester, driven by the drop in SVR and increased maternal blood volume.[6] By 24 weeks, there is a 45% increase in cardiac output over baseline, and this rises to between 60% and 80% within the hour after delivery secondary to increased venous return and maternal autotransfusion. Cardiac output does not drop to normal prepregnancy values until 3 months to 6 months postdelivery.[11,26,29] Increased sympathetic tone increases maternal heart rate by 10 beats per minute (bpm) to 20 bpm, but stroke volume is the driving force behind the rise in cardiac output.[30–32]

Respiratory Changes

Much like the cardiovascular system, the respiratory system undergoes dramatic changes in order to efficiently transport oxygen to and offload carbon dioxide from the fetal-placental unit. Fetal offloading of carbon dioxide is dependent on a diffusion differential from the fetal umbilical arteries to the maternal venous system. In order for this to be accomplished, the respiratory physiology alters to create a state of alkalosis mediated by a drop in arterial P_{CO_2} and by compensatory excretion of bicarbonate by the kidneys.[33,34] There is an approximate 20% increase in oxygen consumption, which is accomplished by increasing both tidal volume and resting minute volume.[35] The functional residual capacity decreases by 20% due to a decrease in both expiratory reserve and residual volume, which puts pregnant women at risk for hypoxia due to lower oxygen reserves.[6,36] Perceived hyperventilation is driven by progesterone and can lead to the sensation of dyspnea in up to 70% of women by 30 weeks' gestation.[6] Most importantly, from a drug metabolism standpoint, is the reduced buffering capacity of the system and the shift in the oxygen-dissociation curve to the right to ensure offloading to the fetoplacental unit.[35,36]

Gastrointestinal and Hepatic Changes

From a pharmacologic standpoint, the important changes in the gastrointestinal system that potentially could alter absorption, distribution, and excretion include a decrease in serum albumin secondary to hemodilution (and some renal excretion), altering drug binding. As each organ system

receives an incremental increase in the proportion of cardiac output, so too does the liver, which either can increase or decrease drug clearance depending on the medication involved.[37] The cytochrome P450 enzymes are up-regulated, which changes the metabolic clearance of many drugs, including some cardiovascular medications.[37,38] Gastric acidity also is increased due to increased placental production of gastrin.[6,39] This coupled with decreased sphincter tone leads to increased rates of reflux. In and of itself this does not interfere with drug metabolism and absorption but the treatment—antacids—can decrease bioavailability of many cardiac medications.[40] Altered α_1-acid glycoprotein along with an increase in fatty acids and lipids can displace bound drugs and increase the unbound drug fraction.[41]

Renal Changes

The drop in SVR affects the renal vasculature with a concomitant dilatation of the renal arterial system as the result of rising progesterone levels. Progesterone likewise mediates resistance to certain angiogenic factors, such as angiotensin II, ensuring the vasodilatory effects are not mitigated.[42] Relaxin stimulates formation of endothelin, which in turn mediates vasodilation of the renal arteries via nitric oxide synthesis.[23,43] This hormonally driven drop in blood pressure coupled with increasing blood volume creates a state of underfilling that is unique to pregnancy, signaling the osmostat to increase water absorption despite a continued rise total body water.[44] Decreased SVR despite rising plasma volumes is only physiologically possible because 80% of the volume increase is within the maternal venous system.[42] With the increasing cardiac output to the renal arteries, there is an increase in glomerular filtration by 50% by the end of the first trimester.[45] As a result, creatinine clearance increases and serum creatinine levels fall, both of which can significantly affect the metabolism and clearance of many cardiac medications.[44] Drug clearance also can be affected by the increasing albumin excretion as the result of increased glomerular permeability.[46] Despite an increase in fractional excretion of albumin, the normal concentration in the urine should not exceed 300 mg/d.[47]

MATERNAL PHARMACOKINETIC ALTERATIONS DURING PREGNANCY

All of the aforementioned physiologic changes contribute to altered drug distribution and their clinical effect during pregnancy. Delayed gastric emptying and increased gastrin production can lead to altered drug absorption and lowered tissue distribution. For example, prolonged gut transit can decrease the absorption of metoprolol or verapamil, and drugs that require an acidic environment may have higher bioavailability leading to toxicity.[48] Pregnant women tend to have more gastric reflux, which can lead to higher consumption of chelators, such as antacids, inadvertently altering cardiac drug metabolism.[49] Higher serum albumin levels lead to higher levels of bound drugs, decreasing the metabolically active free-form and subsequent decreased mechanism of action on the target tissue.[50] Increased glomerular filtration rate (GFR) and renal clearance also can lead to lower drug concentrations, as discussed previously. The increased blood flow to the liver with increased hepatic enzyme activity can alter the doses of certain cardiac medications leading to a change in dosing requirements in order to have the desired effects.[51,52]

PLACENTAL CONTRIBUTION TO PHARMACOKINETICS

The placenta was long held to be a senescent organ, functioning as both a barrier to toxic substances and a transport mediator for nutrients to the growing fetus. In vivo studies, however, have found that the placenta is active in both transport and metabolism of many xenobiotics in the maternal circulation, and these factors should be considered when dosing maternal medications.[53] Other important considerations include the solubility and lipophilic nature of the drug being given, because many drugs easily cross the placental barrier by diffusion and become trapped in the fetal compartment as a result of the lower pH in both the amniotic fluid and fetal blood.[37,53,54] This leads to ionization and accumulation of basic drugs within the fetal system and studies of cord blood analysis at birth have shown that certain medications concentrate in the fetal blood stream compared with the maternal system. In general, uncharged, unionized molecules with high lipid solubility and lower molecular weights readily can cross the placental barrier.[53,55] Solute levels also play a key role in maternal and fetal concentrations, which can change dramatically with the previously described changes within the maternal cardiovascular system. Active transport is accomplished through several different membrane-bound transporters and, although they do not play a significant role in the movement of nutrients and wastes, they can be targets for transplacental drug transfer. During the first trimester, a member of the adenosine triphosphate–binding cassette superfamily (ABC) plays a critical role in eliminating medications from the fetal compartment, and many cardiac

medications, such as verapamil, can inhibit its function.[55,56] The placenta possesses metabolizing enzymes for both phase I (drug oxidation, reduction, and hydrolysis) and phase II (conjugation) reactions that can substantially alter drug levels and transport across the placenta.[53,56]

CLASSIFICATION OF CARDIOVASCULAR MEDICATIONS

Most of the fetal organs fully developed have by the end of the first trimester, which is the epoch in pregnancy referred to as organogenesis.[57] This is the time frame wherein the fetus is most susceptible to teratogens. Most medications are not teratogenic when used in therapeutic doses, but, again, due to the rapidly changing physiology of pregnancy, medication levels can inadvertently rise causing unwanted side effects. The baseline risk for congenital malformations is 1% to 3%.[58] Of these, up to 10% can be attributed to medication use during pregnancy.[58] The US Food and Drug Administration previously had categorized medication risk in pregnancy according to letters (A, B, C, D, and X) with category A medications posing no substantial risk to the fetus and category X medications contraindicated due to the high risk of teratogenicity.[59] Due to the ambiguity of such classification, however, a newer risk stratification model was adopted entitled the Pregnancy and Lactation Labeling Rule, whereby drug applications submitted after June 2015 were categorized according to this new model.[59] The newer labeling removed the dichotomization of the antepartum and labor and delivery time frames and has a new subsection for persons of reproductive potential.[60] The newer labeling is meant to provide more general information, including medication (pregnancy) registries, fetal risks, and the likelihood of developmental abnormalities. In addition, clinical considerations regarding timing, dose, and duration of exposure with both animal and human data are included. It no longer is recommended to use the previous letter classification for clinical decision making.[61] Use of medications during pregnancy is not without some level of risk, and discussing the potential outcomes should be part of the counseling of women with cardiovascular disease who desire to become or who already are pregnant.

The following sections delineate the most commonly used medications in pregnancy and their safety profiles.

ANTIARRHYTHMIC THERAPIES

Maternal cardiac arrhythmias during pregnancy are a common occurrence and treatment should be considered thoughtfully from both obstetric and electrophysiologic standpoints. Ventricular arrhythmias, although rare, represent an emergency, and unstable patients should be treated immediately with electrical cardioversion. Atrial arrhythmias, however, are more common and likely are due to the overall increase in cardiac output and blood volume.[62] Medications frequently are indicated in these patients more so for symptom control rather than for an acute emergency. Pregnant women at risk for arrhythmias include those with prior structural heart disease and those who have had prior cardiac surgery due to congenitally corrected lesions. A careful history should be obtained prior to initiating any antiarrhythmic drugs, because some medications, such as sotalol or flecainide, can cause unwanted maternal drug-drug interactions or side effects. Physicians must consider both adverse maternal and fetal side effects. Patients with underlying preexcitation on EKG should avoid the use of verapamil and digoxin to avoid promoting conduction down an accessory pathway. Careful consideration in the pregnant patient should be taken with digoxin because it has reduced drug effect on the mother during pregnancy due to increased drug clearance and increased unbound fraction of digoxin.[63,64] Due to a digoxin-like substance reported in the maternal serum, digoxin serum levels are not as reliable as in the nonpregnant population.[65] In addition, digoxin is cleared renally and, due to the 50% increase in renal blood flow during pregnancy, may require dosage adjustments. Adenosine also may require increased dosages in pregnancy.

The fetal effects of antiarrhythmic drugs are important to understand and more frequent monitoring may be necessary. Flecainide has an overall good safety profile and is used widely throughout gestation.[66–69] There are some small case reports, however, of flecainide associated with neonatal prolonged QT and heart failure at toxic levels and decreased fetal heart rate variability on external fetal cardiac monitoring.[52] Adenosine does not cross the placenta and has a short half-life and, therefore, is thought to pose minimal risk.[52] Significant fetal effects have been reported after the use of amiodarone, including hypothyroidism and neurodevelopmental complications, making it a last resort in the treatment of arrhythmias.[61] β-Blockers are a commonly used medication for rate control (discussed later). As a class, they usually are considered safe without an increase in congenital cardiac abnormalities, and first trimester use has not been found to be associated with a higher risk of any specific congenital anomalies.[70–73] There are numerous studies looking at

fetal growth restriction (FGR) and β-blockers, including 1 study showing FGR in a group of patients taking propranolol, metoprolol, atenolol, or bisoprolol compared with control.[74,75] Atenolol was associated most strongly with FGR and, therefore, should be avoided in pregnancy.[76]

Use of these medications while breastfeeding is an important consideration when discussing medication options in the postpartum period. Some medications, although contraindicated during pregnancy, can be used safely during breastfeeding and lactation. Most antiarrhythmic medications, including β-blockers, calcium channel blockers, digoxin, flecainide, lidocaine, mexiletine, procainamide, propafenone, quinidine, and sotalol, are compatible with breastfeeding because they have little transfer into the breast milk.[77] It is unknown if adenosine transfers to the breast milk. Amiodarone is a bit more controversial and requires a conversation with the patient prior to initiation. If a patient is on amiodarone and wishes to breastfeed, the infant's pediatrician should be alerted so that neonatal plasma levels can to be monitored because breast milk and infant serum levels are somewhat unpredictable, likely due to the long half-life.[78]

ANTICOAGULATION AND ANTIPLATELET THERAPY

Maternal Issues

Anticoagulation and antiplatelet medications are prescribed commonly in both cardiology and obstetrics for various reasons. An understanding of the hypercoagulable state of pregnancy is paramount because it may change the indication, dosing, and frequency of certain medications. Although anticoagulation commonly is used in the obstetrics realm for thrombophilia or prophylaxis after surgery, a pregnant patient with a mechanical valve is an uncommon situation, which may involve multidisciplinary discussion regarding use and safety. Due to the thrombogenic propensity of pregnancy, these people are at increased risk for valve thrombosis.[79] As well, the changing volume of distribution creates significant challenges in regard to therapeutic windows, putting them at risk for a venous thrombus embolism or hemorrhage, and these women should be monitored more regularly.[61] The risk of valve thrombosis depends on the type and position of the mechanical valve with lower pressure positions (mitral valve) being at higher risk for thrombosis.[79] The risks of fetal teratogenesis with warfarin need to be weighed against the relatively high risk of valve thrombosis with the use of first-trimester heparin, and which modality to use should be a joint discussion between the patient, the obstetrician and the cardiologist. The use of low-molecular-weight heparin (LMWH) is associated with less risk of valve thrombosis than unfractionated heparin but still higher than with vitamin K antagonists (VKAs).[79] The higher risk of valve thrombosis with heparin use likely is secondary to its increased excretion in the maternal kidneys as a result of the higher GFR in pregnancy, because heparin is known to be excreted renally. Meticulous monitoring of anti-Xa levels (rather than partial thromboplastin time) should be employed and followed by an experienced cardiologist or maternal-fetal medicine specialist because these patients are at increased risk for both subtherapeutic and supratherapeutic levels due to these physiologic changes. According to the European Society of Cardiology 2018 guidelines, the use of VKAs throughout pregnancy, under strict international normalized ratio control, is the safest regimen to prevent valve thrombosis.[61] Concomitant aspirin use for valve thromboprophylaxis is recommended by the American College of Cardiology (ACC) and the American Heart Association (AHA) and has been shown to be safe for both mom and fetus alike.[52] It also is used widely in the high-risk obstetrics population to mitigate the risk for preeclampsia.[80] Studies have shown there is no evidence that low-dose aspirin alone increases maternal or fetal bleeding risks, risk of placental abruption, or complications at the time of neuraxial anesthesia during delivery. The risk of bleeding, however, when combined with other anticoagulants has led the ESC guidelines, in contrast to the AHA/ACC guidelines, to not recommend use of low-dose aspirin for mechanical valves.[61,81–83]

Fetal Issues

Warfarin embryopathy is a significant morbidity associated with VKAs.[84] First-trimester transplacental passage increases the risk for fetal warfarin syndrome or Di Sala syndrome.[85] The most common teratogenic findings include facial dysmorphisms, such as nasal hypoplasia, skeletal abnormalities (limb hypoplasia and stippled epiphyses), central nervous system abnormalities (ventral and dorsal midline dysplasia), and cardiac defects.[84–88] In the second and third trimesters, there is a 0.7% to 2% risk of ocular/central nervous system abnormalities and intracranial hemorrhage with VKAs.[61] There are higher rates of miscarriage and stillbirth reported when daily doses exceed 5 mg.[89] Current guidelines recommend women who are taking this dose or higher during the first trimester to be transitioned to

LMWH or unfractionated heparin by the end of the sixth week of gestation to decrease the risk of fetal malformations.[83] In women on warfarin who present in labor, the recommendation is to consider cesarean delivery to avoid neonatal intracranial hemorrhage.[90] During the last week of gestation, it is not unreasonable to admit patients and have them on a heparin drip in either anticipation of spontaneous labor or for a planned induction. Heparin and LMWH both are large molecules and do not cross the placenta. Given the changing volume of distribution in pregnancy along with increase excretion of these medications through higher GFR, both peak and trough levels should be monitored throughout pregnancy. A meta-analysis of maternal and fetal outcomes in more than 800 women with mechanical heart valves utilizing different anticoagulant strategies found that VKAs were associated with the lowest risk of adverse maternal outcomes, whereas the use of LMWH was associated with the lowest risk of adverse fetal outcomes.[79]

There are minimal human data on the teratogenic effects of aspirin use in the first trimester.[77] Case-control studies of children with congenital heart defects found no association between these abnormalities and maternal use of aspirin.[91,92] A meta-analysis did not find an increased risk of congenital defects associated with first trimester use of aspirin and a prospective study of more than 50,000 pregnancies did not report aspirin-associated malformations, altered birth weight, or perinatal deaths.[93,94] High-dose aspirin and near-term use of aspirin and other prostaglandin synthase inhibitors may result in closure or constriction of the fetal ductus arteriosus with resultant pulmonary hypertension.[95]

There are several case reports of clopidogrel used during pregnancy without documented congenital defects although sufficient data to determine absolute safety are lacking.[96–98] There are insufficient data to recommend direct oral anticoagulants for women in pregnancy and few data in regard to prasugrel, ticagrelor, abciximab, or eptifibatide; therefore, their use is not recommended.[52]

Breastfeeding and Lactation

Although there are variations in the ability of these medications to transfer to breast milk, there are few absolute contraindications to their use. Aspirin is excreted in the breast milk and likely is safe at a lower doses.[77] Prasugrel and ticagrelor have been shown to transfer in rat studies but, overall, as with clopidogrel, their effect largely is unknown.[99] Warfarin has only minimal transfer and generally is considered safe.[77,89] Unfractionated heparin and enoxaparin largely are considered safe but the amount that crosses into breast milk is unknown.[77]

HYPERTENSIVE DISORDERS AND PREECLAMPSIA: RECOMMENDED TREATMENT

Hypertensive disorders of pregnancy (HDPs) affect up to 10% of all pregnancies in the United States and the rates continue to climb.[100] Due to the rising rates of obesity, women entering pregnancy with comorbid chronic hypertension also are on the rise. Chronic hypertension, or elevated blood pressure, either prior to pregnancy or as a new diagnosis, defined by 2 blood pressures of 140 mm Hg systolic or higher and/or 90 mm Hg diastolic or higher separated by 4 hours prior to 20 weeks, complicates 3% of all pregnancies and, therefore, makes up a large portion of the morbidity associated with adverse pregnancy outcomes.[100,101] Definitions are important because they dictate management, timing of delivery, and treatment recommendations. As well, outcomes for different HDPs are varied, with more severe events occurring in women with higher recorded blood pressures. For instance, women with gestational hypertension (new-onset elevated blood pressures as defined by a systolic pressure of 140 mm Hg or higher and/or a diastolic pressure of 90 mm Hg or higher on 2 occasions separated by 4 hours without proteinuria or any other signs of end-organ damage) have lower rates of adverse outcomes including small for gestational age infants and maternal stroke as well as lower rates of recurrence of HDPs in any future pregnancies.[100,102–104] As well, the American College of Obstetricians and Gynecologists does not recommend that women with gestational hypertension receive antihypertensive treatment because studies have not shown an improvement in outcomes with treatment and, because up to 50% of women with gestational hypertension progress to preeclampsia, treatment would be masking any worsening disease.[104] Severe disease should be treated, however, once a diagnosis has been established. Preeclampsia has been redefined and now women with new-onset elevated blood pressures of 140 mm Hg systolic and/or 90 mm Hg on 2 occasions separated by 4 hours after 20 weeks' gestation with proteinuria now are reclassified as preeclamptics without severe features.[104] Preeclampsia with severe features has numerous laboratory and clinical inclusion criteria. For the treating cardiologist, the most important change is that preeclampsia with severe features

(previously known as severe preeclampsia) can be defined by blood pressures alone, despite being aproteinuric.[101,104] Any new-onset severe range blood pressures, defined by systolic of 160 mm Hg or greater and/or diastolic readings of 110 mm Hg or greater separated within minutes, can qualify as pr-eclampsia with severe features.[104] Although women with gestational hypertension or preeclampsia without severe features are managed without antihypertensive therapy on an outpatient basis, it is recommended that women with preeclampsia with severe features remain in the hospital until delivery and receive antihypertensive therapy to prevent adverse maternal outcomes, such as worsening hypertension and stroke.[3,104,105]

Usually, a cardiologist is asked to become involved to manage chronic hypertension prior to 20 weeks or during the postpartum period when fluid shifts and autotransfusion after delivery can exacerbate HDPs. It, therefore, is important to have knowledge regarding the safety profiles of the most commonly used antihypertensives for both pregnancy and lactation.

Treatment of hypertensive Disorders of Pregnancy: Recommended Antihypertensive Medications

Although β-blockers are considered fourth-line therapy outside of pregnancy, due to their fetal and neonatal safety profile, labetalol is the first-line agent recommended for the treatment of both chronic hypertension and acute hypertensive emergencies throughout gestation.[100,104–106] Labetalol is a nonselective α_1-, β_1-, and β_2-adrenergic blocker, which lowers blood pressure by peripheral vasodilation and has not been shown to have teratogenic effects when used in the first trimester despite its ability to cross the placenta.[107] It has been associated with maternal hypotension, fetal bradycardia, perinatal jaundice, and neonatal hypoglycemia.[70,108,109] There is the association of low birth weight with the use of labetalol; however, this likely is independent of drug use and rather a manifestation of the hypertension itself.[110] Although it has been found in the maternal breast milk, it generally is considered safe for the neonate.[111] Labetalol is recommended as first-line therapy for women with chronic hypertension planning a pregnancy and for the acute treatment of severe hypertension secondary to either chronic hypertension exacerbation or preeclampsia with severe features (intravenous dosing only).[100,104] Due to the increased volume of distribution, labetalol may require 3-times daily dosing during pregnancy. Metoprolol has a similar safety profile to labetalol but a longer onset of action, which is not ideal for acute hypertensive emergencies in pregnancy. Women treated for underlying chronic hypertension on metoprolol can continue with their current medication regimen, however, keeping in mind that metoprolol has a higher clearance rate in the second and third trimesters and may require aggressive adjustments in dosing/frequency in order to maintain a therapeutic window.[112] Both have long-term follow-up studies in children exposed in utero with no associated adverse health outcomes.[113,114]

Hydralazine is a potent arterial vasodilator that is recommended as a second-line alternative to labetalol for the treatment of acute hypertensive urgencies during pregnancy.[104,105] Hydralazine does, however, have a higher risk for hypotension compared with oral nifedipine or intravenous labetalol and should be taken into consideration when administering due to the risk for uterine hypoperfusion and subsequent non-reassuring fetal status.[115] There are no associated risks for birth defects when used in the first trimester and it is considered safe for breastfeeding mothers.[107,116]

Calcium channel blockers are categorized as either dihydropyridines or nondihydropyridines. Nifedipine, a dihydropyridine, is used widely in pregnancy for control of chronic hypertension, acute hypertensive emergencies, and uterine tocolysis.[100,104,117] It has been shown more effective at lowering and maintaining blood pressure in an acute hypertensive crisis than hydralazine and its rapid onset of action makes it ideal for women without intravenous access or with contraindications to β-blockade.[104,115,118] Nifedipine is considered safe during the first trimester and does not pose an increase in teratogenic risk.[119]

Methyldopa is an α_2-receptor agonist with a long track record of safety in pregnancy. Although previously the first-line agent, its longer onset of action precludes it from being used in hypertensive urgencies.[120] Women with chronic hypertension who come into pregnancy well-controlled on methyldopa may continue using it but again should be aware that due to the increased volume of distribution may require more frequent and/or increased dosing.[121] It has not been associated with any fetal, neonatal, or maternal adverse outcomes.[122]

Antihypertensive Medications To Be Used with Caution

Amlodipine, another dihydropyridine, has not been used widely in pregnancy and, therefore, there are minimal safety data reported. There are some case series, however, reporting an increase in seizure

activity in neonates exposed in utero and variable reports on birth defects and neurodevelopmental outcomes.[123] Although not contraindicated, amlodipine should be considered only in refractory cases or when contraindications to other, safer options are present.

Diuretics are utilized judiciously outside of pregnancy for the control of hypertension through reduced preload and plasma volume. The normal physiology of pregnancy dictates that plasma volume and, thereby, uterine artery blood flow increase in order to transfer nutrients to the growing fetus, which is counterintuitive to the mechanism of action for diuretics. Thiazide diuretics can cross the placenta and have been associated with neonatal jaundice, thrombocytopenia, hyponatremia, and fetal bradycardia.[65] Hydrochlorothiazide and furosemide are not associated with birth defects but, due to the risk for uterine hypoperfusion, should not be initiated during pregnancy for the treatment of hypertension; women who enter into pregnancy with underlying heart failure on these medications do have the option of continuation.[65] The development of preeclampsia—an intravascularly volume deplete disease state—and concomitant use of diuretics should be approached with extreme caution because this will further decreases end-organ perfusion.

Diltiazem commonly is used in women with underlying renal dysfunction due to its purported renal-protective properties and has minimal transfer across the placental barrier.[124] There are some reports of increased fetal loss; therefore, it should not be started as a first-line agent in the first trimester.[119]

SUMMATION

Reducing maternal morbidity and mortality is an essential public health initiative that requires partnerships across all medical specialties. Because cardiologists and obstetricians collaborate in the care of women with congenital and acquired heart disease, a significant shift toward improved outcomes undoubtedly will be seen. Possessing a basic knowledge of safe medication use in the care of this population aids the practitioner in providing safe guidance to women throughout the puerperium. The lack of randomized control trials will continue to present a challenge in pharmaceutical guidelines for pregnancy, but registries, case studies, and retrospective analyses may assist in filling this knowledge gap.

DISCLOSURE

The authors have nothing to disclose.

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