JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 4, 2019

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Use of Medication for Cardiovascular Disease During Pregnancy

JACC State-of-the-Art Review

Dan G. Halpern, MD,[a] Catherine R. Weinberg, MD,[a] Rebecca Pinnelas, MD,[a] Shilpi Mehta-Lee, MD,[b] Katherine E. Economy, MD,[c] Anne Marie Valente, MD[d]

JACC JOURNAL CME/MOC/ECME

This article has been selected as the month's *JACC* CME/MOC/ECME activity, available online at http://www.acc.org/jacc-journals-cme by selecting the *JACC* Journals CME/MOC/ECME tab.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 Medical Knowledge MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Use of Medication for Cardiovascular Disease During Pregnancy: *JACC* State-of-the-Art Review will be accredited by the European Board for Accreditation in Cardiology (EBAC) for 1 hour of External CME credits. Each participant should claim only those hours of credit that have actually been spent in the educational activity. The Accreditation Council for Continuing Medical Education (ACCME) and the European Board for Accreditation in Cardiology (EBAC) have recognized each other's accreditation systems as substantially equivalent. Apply for credit through the post-course evaluation. While offering the credits noted above, this program is not intended to provide extensive training or certification in the field.

Method of Participation and Receipt of CME/MOC/ECME Certificate

To obtain credit for *JACC* CME/MOC/ECME, you must:

1. Be an ACC member or *JACC* subscriber.
2. Carefully read the CME/MOC/ECME-designated article available online and in this issue of the *Journal*.
3. Answer the post-test questions. A passing score of at least 70% must be achieved to obtain credit.
4. Complete a brief evaluation.
5. Claim your CME/MOC/ECME credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) identify which anti-arrhythmic drugs for supraventricular tachycardia are safe in pregnancy, and prioritize their use according risk profile of mother and fetus; 2) select an appropriate anticoagulation regimen for patients with mechanical valves during pregnancy and lactation; 3) discuss and select appropriate therapy for women with Marfan syndrome during pregnancy; 4) identify an appropriate antihypertensive regimen in pregnant women with chronic hypertension; 5) discuss the various antilipemic agents and their compatibility with pregnancy; and 6) diagnose peripartum cardiomyopathy and choose the best treatment strategy based on available evidence.

CME/MOC/ECME Editor Disclosure: *JACC* CME/MOC/ECME Editor Ragavendra R. Baliga, MD, FACC, has reported that he has no financial relationships or interests to disclose.

Author Disclosures: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME/MOC/ECME Term of Approval

Issue Date: February 5, 2019
Expiration Date: February 4, 2020

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Adult Congenital Heart Disease Program, Cardiology Division, NYU Langone Health, New York, New York; [b]Division of Maternal Fetal Medicine, Department of Obstetrics & Gynecology, New York University Langone Health, New York, New York; [c]Pregnancy and Cardiovascular Disease Program, Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and the [d]Boston Adult Congenital Heart Disease Program, Boston Children's Hospital and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 15, 2018; revised manuscript received October 19, 2018, accepted October 23, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.10.075

JACC VOL. 73, NO. 4, 2019
FEBRUARY 5, 2019:457–76

Use of Medication for Cardiovascular Disease During Pregnancy

JACC State-of-the-Art Review

Dan G. Halpern, MD,[a] Catherine R. Weinberg, MD,[a] Rebecca Pinnelas, MD,[a] Shilpi Mehta-Lee, MD,[b] Katherine E. Economy, MD,[c] Anne Marie Valente, MD[d]

ABSTRACT

Cardiovascular disease complicating pregnancy is rising in prevalence secondary to advanced maternal age, cardiovascular risk factors, and the successful management of congenital heart disease conditions. The physiological changes of pregnancy may alter drug properties affecting both mother and fetus. Familiarity with both physiological and pharmacological attributes is key for the successful management of pregnant women with cardiac disease. This review summarizes the published data, available guidelines, and recommendations for use of cardiovascular medications during pregnancy. Care of the pregnant woman with cardiovascular disease requires a multidisciplinary team approach with members from cardiology, maternal fetal medicine, anesthesia, and nursing. (J Am Coll Cardiol 2019;73:457–76)

Cardiovascular disease (CVD) is the most common cause of indirect maternal mortality during pregnancy, affecting 1% to 2% of pregnancies and accounting for 15.5% of maternal deaths in the United States (1,2). Increased age of first pregnancy, rising numbers of women with cardiovascular risk factors such as obesity, hypertension, and diabetes, as well as a growing population of women of reproductive age that have congenital heart disease, have led to an increased burden of CVD in pregnancy (3,4). According to the ROPAC registry (Registry of Pregnancy and Cardiac Disease), up to one-third of women with CVD use cardiac medications during pregnancy, and this use was associated with increased fetal risk such as intrauterine fetal growth restriction (IUGR) (5). Beta-blockers were the most commonly used CVD medications, followed by antiplatelet and diuretic agents (5). Pharmacological therapy for CVD during pregnancy is challenging because the pharmacokinetics of a drug may change throughout gestation. The majority of data on the safety of medication use during pregnancy relies on observational studies and expert opinion. The purpose of this state-of-the-art review is to provide an update on the current evidence and recommendations for the use of medications in pregnancy in women with CVD.

HEMODYNAMIC CHANGES OF PREGNANCY

Complex and dynamic physiological changes occur during pregnancy (**Figure 1**). These adaptations continue as the fetus grows and develops, peaking at the time of labor and delivery, and continuing through the postpartum period. Healthy women can adapt without significant consequences, whereas in women with underlying cardiac conditions, these changes may unmask a previously unknown condition or exacerbate existing abnormal hemodynamics. In early pregnancy, there is an increase in red blood cell mass. Estrogen activates the renin-angiotensin-aldosterone systems, increasing plasma volume (up to 40% of the prepregnancy value) and promoting sodium and water retention (6,7). The disproportionate increase in volume leads to hemodilution and results in the physiological anemia of pregnancy. To accommodate the increase in volume, vasodilatation and vascular remodeling occur with a reduction in both the systemic and pulmonary vascular resistance. By the second trimester, the systemic vascular resistance falls by 30% to 50% from pre-pregnancy values, followed by a slight increase at the end of the third trimester. Relaxin, prostacyclin, and possibly nitric oxide also contribute to a fall in blood pressure, beginning as early as 6 to 8 weeks. Cardiac output initially increases as a result of an increase in stroke volume. Later in gestation, heart rate increases 10 to 20 beats/min, reaching a maximum in the third trimester. The net effect of these physiological changes is increased cardiac output 30% to 50% above the prepregnancy level in a singleton gestation and as much as an ~15% further increase for twin pregnancies (8).

At the time of labor and delivery, heart rate and circulating catecholamines increase, and there is 300 to 500 ml of blood delivered into the circulation with

each uterine contraction. Immediately postpartum, autotransfusion from the uteroplacental circulation and increased venous return due to decompression of the inferior vena cava further raise central venous pressure. Cardiac output increases by up to 50% to 80% postpartum compared with prelabor values (8). These changes begin to resolve within the first 48 h. Most changes resolve within the first 2 weeks, however, it may take as long as 6 months to see a full return to baseline (9). During labor and the early postpartum period, patients are most vulnerable to cardiovascular complications due to these profound hemodynamic changes.

PHARMACOKINETICS DURING PREGNANCY

Pharmacokinetics in pregnancy are altered as a result of physiological changes that take place throughout gestation and the postpartum period. Delayed gastric emptying and motility, increased plasma volume and fat accumulation, increased volume of distribution (Vd), decreased albumin and plasma binding proteins, increased minute ventilation, and increased hepatic and renal clearance, all may affect drug distribution and clearance (10) (**Figure 1**). The sum of these changes commonly results in a reduced pharmacological effect of the drug; however, there are exceptions. Few studies have directly studied the properties of cardiovascular drugs in pregnancy compared with the nonpregnant state.

ABSORPTION. During pregnancy, increases in progesterone delay intestinal motility in the small bowel, and nausea and vomiting may inhibit absorption of medications (11,12). The use of antacids and iron supplements may further decrease the bioavailability of a drug due to chelation in the setting of increased gastric pH (13). However, these changes are mainly theoretical, because several studies of cardiac drugs, including sotalol and propranolol, have shown no difference in bioavailability compared with the nonpregnant state (14–16).

VOLUME OF DISTRIBUTION. The 50% increase in plasma volume and total body water increases the Vd of hydrophilic and lipophilic substances (17). As Vd rises throughout pregnancy, the initial and peak concentrations of a drug may decrease, requiring an increase in dosage. The half-life of drugs is variable and depends on both Vd and clearance by the different organ systems (i.e., lungs, kidneys, and liver) (16). Vd is also affected by the amount of drug bound to plasma proteins (e.g., albumin). Therefore, the net exposure of a drug during pregnancy depends on the interplay between Vd, degree of binding to serum proteins, extraction ratio, and clearance.

HEPATIC CLEARANCE AND METABOLISM. Hepatic extraction ratio (ER) refers to the fraction of drug removed from the circulation by the liver. High ER drugs such as propranolol, verapamil, and nitroglycerin are quickly taken up into hepatocytes, and their clearance depends on the rate of blood flow to the liver. In pregnancy, perfusion to the liver stays stable or increases, causing high ER drugs to be metabolized faster, which in turn may require an increase in drug dosing (18). Clearance of low ER drugs such as warfarin does not depend on the hepatic blood flow, but rather on intrinsic hepatic activity, as well as on the unbound fraction of the drug in plasma.

Within the liver, enzymes involved in both phase I (oxidation, reduction, hydrolysis) and phase II (conjugation) metabolism are altered during pregnancy (18,19). The reasons for changes in hepatic elimination are closely related to both estrogen and progesterone activity. Progesterone stimulates hepatic microsomal enzyme activity, whereas estrogen's cholestatic effects may interfere with drug clearance, and both competitively inhibit microsomal oxidase (12).

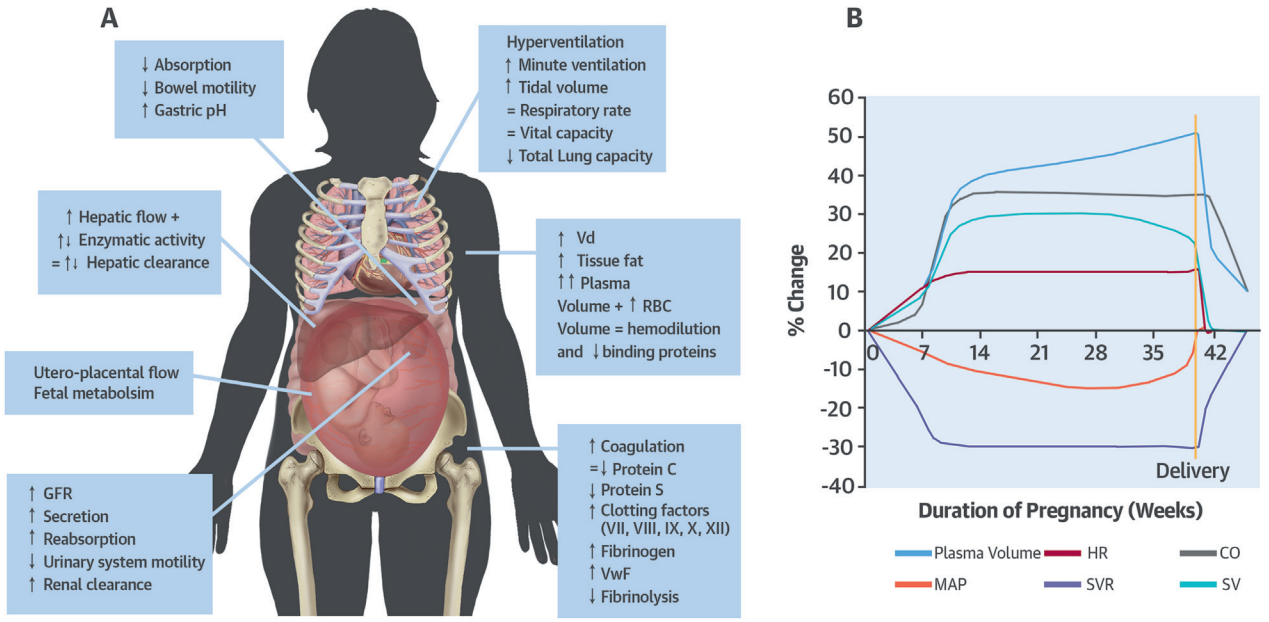
Cytochrome P450 enzymes involved in phase I metabolism are mostly up-regulated during pregnancy but may have variable effects. Genetic polymorphisms may affect metabolism beyond the increased effect conferred by pregnancy. Nifedipine and metoprolol are catalyzed by CYP3A (20) and CYP2D6 (21), respectively. Both enzymes are induced in pregnancy, and therefore, drug levels are reduced compared with the nonpregnant state. CYP2C9 together with vitamin K epoxide reductase activity levels affect the dose of warfarin needed during pregnancy. Labetalol is an example of a drug that owing to up-regulated phase II metabolism glucuronide conjugation, has a shorter half-life during pregnancy (22).

RENAL CLEARANCE. Effective renal plasma flow is increased as much as 50% to 85% in pregnancy (23). Glomerular filtration rate increases by 45% to 50% by the end of the first trimester (24) and continues to rise until term with a possible downtrend in the last few weeks. Tubular function is variable with decrease in uric acid and glucose absorption, and increase in excretion of urinary protein and small amounts of albumin (25). Although tubular functions may increase to match renal blood flow, this accommodation

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic medication
ACE = angiotensin-converting enzyme
ACOG = American Congress of Obstetricians and Gynecologists
AF = atrial fibrillation
AMD = alpha-methyldopa
ARB = angiotensin receptor blocker
ARNi = angiotensin receptor-neprysilin inhibitor
BAV = bicuspid aortic valve
CCB = calcium channel blocker
CVD = cardiovascular disease
ER = extraction ratio
ESC = European Society of Cardiology
FC = functional class
FDA = Food and Drug Administration
HCTZ = hydrochlorothiazide
IUGR = intrauterine fetal growth restriction
LMWH = low molecular weight heparin
MFS = Marfan syndrome
PH = pulmonary hypertension
PLLR = Pregnancy and Lactation Labeling Rule
PPCM = peripartum cardiomyopathy
QTc = QT interval corrected for heart rate
RV = right ventricular
SVT = supraventricular tachycardia
Vd = volume of distribution
VKA = vitamin K antagonist
VT = ventricular tachycardia
WPW = Wolff-Parkinson-White

FIGURE 1 Hemodynamic and Pharmacological Changes During Pregnancy



The pharmacokinetic and hemodynamic changes throughout pregnancy. **(A)** System based pharmacokinetic changes throughout pregnancy. **(B)** hemodynamic changes diagram throughout pregnancy. CO = cardiac output; GFR = glomerular filtration rate; HR = heart rate; MAP = mean arterial pressure; RBC = red blood cell; SV = stroke volume; SVR = systemic vascular resistance; Vd = volume of distribution; VwF = Von Willebrand factor. Image in **B** adapted from Fuster V, Harrington RA, Narula J, Eapen ZJ, editors. Hurst's the Heart. 14th edition. New York, NY: McGraw Hill, 2017.

may not be adequate in hypertension and preeclampsia (26,27). In a group of pregnant women treated for hypertension with atenolol, clearance increased by 38% in the second trimester and 36% in the third trimester, with an increase in creatinine clearance as well (28). A limitation to the study was the predominance of obese women in whom a higher creatinine clearance is expected (29).

DRUG CLASSIFICATION IN PREGNANCY

In the 1960s, the teratogenic effect of thalidomide in pregnancy resulted in heightened public concern about the use of medications in pregnancy (30–32). In 1966, the U.S. Food and Drug Administration (FDA) issued a requirement for animal studies, and in 1979, they introduced a 5-tier set of alphabet categories (ABCDX) designed to designate the safety of a drug for use during pregnancy (33). That system was quickly adopted and was used to guide clinicians and patients on the safety of drugs during pregnancy for over 35 years until the FDA replaced those categories with a narrative labeling system in 2015 (**Table 1**). Category A drugs were generally safe to use and Category X were contraindicated, which were easily interpretable categories in clinical medicine. However, the ambiguous safety data and misinterpretation surrounding categories B, C, and, D made them particularly lacking in clinical utility (34). In 2015, the FDA adopted the Pregnancy and Lactation Labeling Rule (PLLR) for all new applications for prescription drugs and biologics after June 30, 2015, when they determined that the ABCDX categories were often confusing and did not accurately or consistently communicate differences in degrees of fetal risk. The rule is being phased in gradually for all prescription drugs approved between June 2001 and June 2015. The new PLLR risk summaries are meant to be written within the context of current available epidemiological data that suggest that major birth defects occur in 2% to 4% of the general population and that miscarriage occurs in 10% of clinically recognized pregnancies (35,36). One of the changes in the PLLR format is to include pregnancy, labor, and delivery in the same labeling and provide separate categories for lactation and male and female reproduction. According to the new European Society of Cardiology (ESC) guidelines, the ABCDX is no longer recommended for decision-making (1).

FETAL TERATOGENICITY

The use of medications during pregnancy requires a thoughtful approach, balancing fetal and maternal risk. Data regarding teratogenicity of drugs are primarily based on animal models, retrospective analyses, advisory boards, or case reports and is overall limited and insufficient. Only a minority of drugs have ever been associated with significant human fetal malformation or demise, yet the medicolegal implications are so great, drug manufacturers will not readily commit to drug safety during pregnancy (37). It is also the timing of administration of the drug that is critical to the development of teratogenicity, and because organogenesis occurs during the first trimester, this is the most vulnerable period. However, some medications exert fetal effect later in pregnancy such as angiotensin-converting enzyme (ACE) inhibitors. Drugs with known teratogenic potential (e.g., captopril or bosentan) should be avoided in favor of safer alternatives, but the use of other medications in pregnancy may be more nuanced.

GENERAL APPROACH TO CARDIOVASCULAR MEDICATIONS IN PREGNANCY AND BREASTFEEDING

The basic principles of medication use in pregnancy and lactation are to determine the necessity, urgency, timing during gestation, and fetal adverse effect of the drug. Because the majority of drugs transfer to the milk, the effects on neonates should be considered. The lowest effective dose should be used. The woman should be counseled on risks and benefits, and provided current data, acknowledging limitations. Internet databases and manufacturers' instructions containing prescribing information are helpful in acquiring the most current information. Maternal fetal medicine specialists should be consulted to assist in medication management during pregnancy, and the pediatrician post-partum during lactation. In the event of a cardiopulmonary arrest, standard ACLS protocols should be followed including use of medications and defibrillation (38).

SPECIFIC MEDICATIONS

The **Central Illustration and Table 2** summarize some of the more common CVD medications used during pregnancy, potential adverse events, former FDA category, and the compatibility of the drug with breastfeeding.

ANTIARRHYTHMIC MEDICATIONS

Maternal cardiac arrhythmias may increase in pregnancy, either arising de novo or due to physiological changes of pregnancy. Increased dilation of the heart chambers as well as the effects of progesterone are considered the primary mechanisms promoting arrhythmia (39). Atrial and ventricular premature contractions and supraventricular tachycardia (SVT) are the most common arrhythmias, whereas atrial fibrillation (AF) is increasing in prevalence with age and in patients with congenital heart disease. Ventricular arrhythmias are much rarer (40). New onset of arrhythmias in a pregnant woman with a structurally normal heart should prompt a search for underlying conditions, such as thyroid disease or pulmonary embolus. Bradyarrhythmias are rare and may be related to uterine compression, increased vagal tone, or structural heart disease and rarely need pacing (41). Because antiarrhythmic medications (AADs) are used in pregnancy for both maternal and fetal conditions, their mechanisms and adverse effect profiles must be tolerable to both mother and fetus. AADs should be avoided if possible during the first trimester, and initiation of the drug should be attempted at the lowest dose with involvement of an electrophysiologist skilled in the management of arrhythmias in pregnancy. As with the nonpregnant patient, hemodynamically unstable arrhythmia should be treated with electric

TABLE 1 FDA's Current Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products

Pregnancy

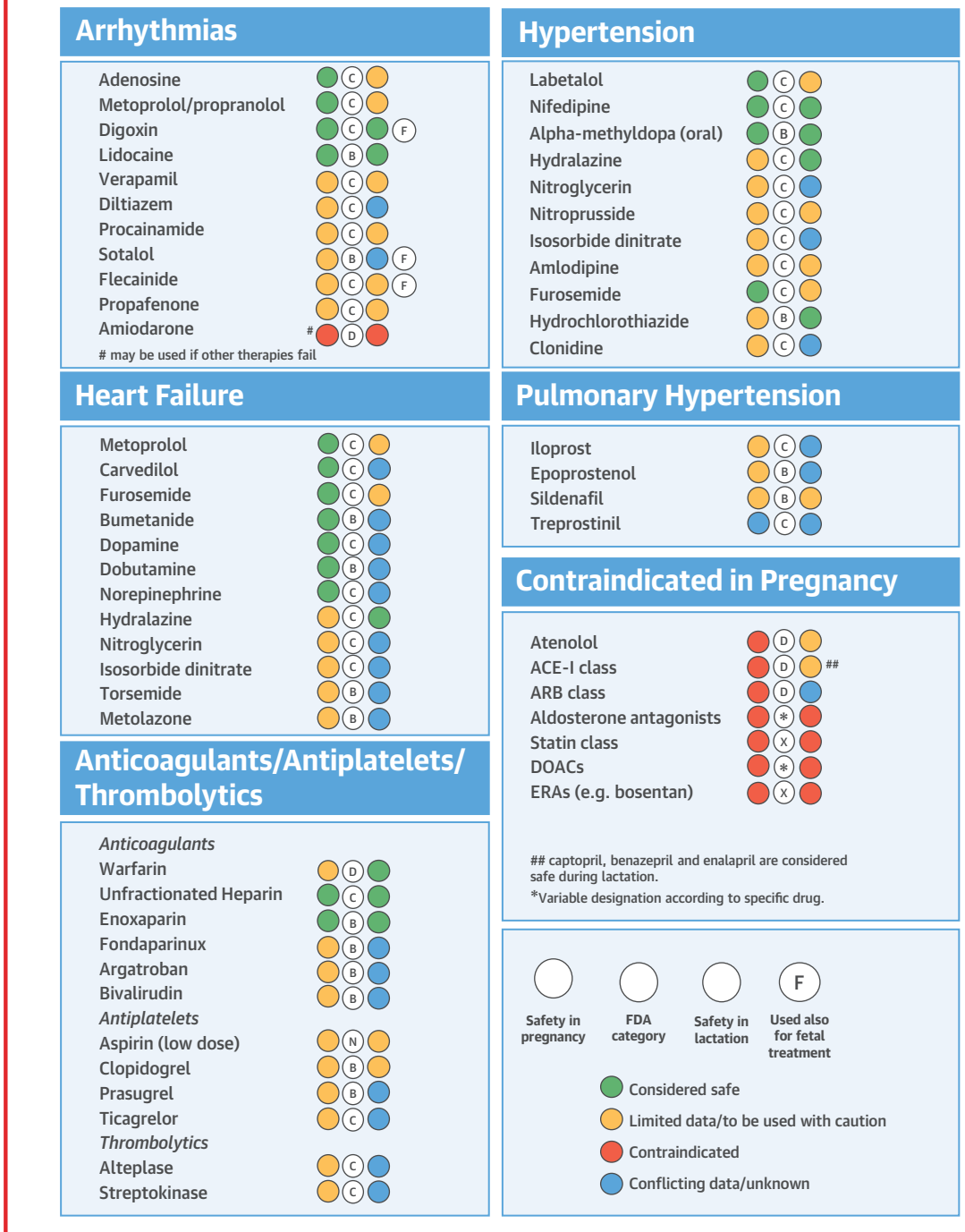
This subsection contains information on pregnancy, including labor and delivery.

Narrative summaries of the risks of a drug during pregnancy and discussions of the data supporting those summaries are required in labeling to provide more meaningful information for clinicians under the following subheadings:

- Pregnancy exposure registry: to inform health care providers of the availability of a pregnancy exposure registry for a product with contact information (e.g., a toll-free telephone number, web 178 site) needed to enroll in or to obtain information about the registry.
- Risk summary: If information on birth defects and miscarriage is available for the patient population for whom the drug is labeled, it must be included. When use of a drug is contraindicated during pregnancy, this information must be stated first.
  - "Structural abnormalities" describes dysmorphology, which includes malformations, variations, deformations, and disruptions.
  - "Embryo-fetal and/or infant mortality" describes developmental mortality, which includes miscarriage, stillbirth, and infant death (including neonatal death).
  - "Functional impairment" describes functional toxicity, which includes such outcomes as deafness, endocrinopathy, neurodevelopmental effects, and impairment of reproduction.
  - "Alterations to growth" describes such outcomes as growth restriction, excessive growth, and delayed and early maturations.
- Clinical considerations
  - Disease-associated maternal and/or embryo/fetal risk;
  - Dose adjustments during pregnancy and the postpartum period;
  - Maternal adverse reactions;
  - Fetal/neonatal adverse reactions;
  - Labor or delivery
- Data
  - Human data;
  - Animal data

FDA = U.S. Food and Drug Administration.

CENTRAL ILLUSTRATION Cardiovascular Medications in Pregnancy



Halpern, D.G. et al. J Am Coll Cardiol. 2019;73(4):457–76.

Former Food and Drug Administration ABCDX categories: A) no demonstrated risk to the fetus based on well-controlled human studies; B) no demonstrated risk to the fetus based on animal studies; C) animal studies have demonstrated fetal adverse effects, no human studies, potential benefits may warrant use of the drug; D) demonstrated human fetal risk, potential benefits may warrant use of the drug; and X) demonstrated high risk for human fetal abnormalities outweighing potential benefit; N) nonclassified. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DOACs = direct oral anticoagulants; ERA = endothelin-receptor antagonists; INH = inhaled; IV = intravenous; PO = by mouth.

cardioversion or defibrillation, which are commonly safe for the fetus. The use of implantable cardioverter-defibrillators is not associated with a significant increase in adverse fetal outcomes or maternal complications (42).

ATRIAL ARRHYTHMIAS. Symptomatic atrial and ventricular premature contractions rarely require treatment, although β-blockers may be used. SVT is the most common sustained arrhythmia in pregnancy with atrioventricular node re-entry tachycardia being the most common mechanism in a structurally normal heart (43). Treatment of SVT includes vagal maneuvers, followed by adenosine, β-blockers (preferably a β1-selective blocker such as metoprolol), and verapamil as third-line therapy. Suppressive therapy for SVT in the absence of pre-excitation may include β-blockers alone or in combination with digoxin, or oral verapamil. Sotalol or flecainide can be considered in women without structural heart abnormalities. Flecainide or propafenone are recommended for the prevention of SVT in patients with Wolff-Parkinson-White (WPW) syndrome (1). Amiodarone is almost never used due its high risk of fetal thyroid and neurodevelopmental complications (see later in the text). Low-dose radiation catheter ablation is a rare last resort for the significantly symptomatic patient.

AF or atrial flutter is observed in women with structural heart disease (e.g., congenital, valvular, cardiomyopathy) with high recurrences during pregnancy. For rate control, β-blockers, verapamil, and digoxin are first-line therapy, and for rhythm control, sotalol, flecainide, or propafenone may be considered. AF in the setting of pre-excitation manifests as a wide-complex tachycardia and is treated with intravenous procainamide. Verapamil and digoxin can promote conduction through accessory pathways and should be avoided in women with pre-excitation. Anticoagulation should be considered in pregnant women with AF/atrial flutter especially with structural abnormalities (e.g., rheumatic mitral valve stenosis); however, risk stratification during pregnancy is controversial, and some sources recommend using the same risk stratification as nonpregnant patients (1).

Adenosine is a nucleoside with a half-life of seconds that has been safely used in treatment of maternal SVT, atrial tachycardia, and orthodromic atrioventricular re-entrant tachycardia in WPW. Rarely, it has been used to differentiate between SVT and VT. Adenosine is generally considered safe in pregnancy although fetal bradycardia has been described (44,45). Adverse effects include bradyarrhythmia, dyspnea, chest pain, and flushing.

β-Blockers are the most widely used medications in pregnancy and have been studied more extensively than other AADs because of their role in treating hypertension, valvular disease, heart failure, atrial and ventricular arrhythmias, and long QT syndrome (1,39). A number of large, retrospective studies have addressed the question of adverse fetal events and abnormalities resulting from exposure to β-blockers. In a retrospective study of 379,238 pregnancies in which 1.3% of patients were exposed to β-blockers, there was no significant increase in congenital cardiac abnormalities after adjusting for maternal factors (46). A European registry of congenital abnormalities found that there was an increased risk of neonatal multicystic renal dysplasia with β-blockers compared with controls, but they did not find increased hypospadias, neural tube defects, heart defects, or oral clefts (47), which were identified in prior studies (48,49). Compared with controls, neonates exposed to β-blockers had significantly more bradycardia (odds ratio: 1.29; 95% confidence interval: 1.07 to 1.55) and hypoglycemia (odds ratio: 1.68; 95% confidence interval: 1.50 to 1.89), even after multivariate adjustment in a Medicaid database of 2,292,116 pregnancies. Labetalol, rather than metoprolol or atenolol, was most associated with these effects (50). There are also studies demonstrating that infants were small for gestational age if exposed to β-blockers (51,52). Additionally, increased risk of preterm birth was observed, with similar results for all β-blockers studied (51).

Atenolol is a hydrophilic drug with renal elimination and carries an FDA category D classification. The ESC guidelines recommend against its use in pregnancy for arrhythmia (1) due to the risk of fetal growth restriction (53,54). There is also a case report connecting antenatal atenolol exposure to retroperitoneal fibromatosis in an infant (55).

Propranolol is generally considered safe in pregnancy, however, in a small study of 12 pregnancies, one-half of the neonates had intrauterine growth retardation. There were also single cases of hypoglycemia, polycythemia, and hyperbilirubinemia (56).

Metoprolol is well-tolerated and used for maternal SVT and ventricular arrhythmias. Clearance during middle and late pregnancy is higher (57); however, in a study with 8 women in the third trimester, the authors found that there was 4 times the heart rate effect and double the systolic blood pressure effect for a given plasma concentration during pregnancy compared with postpartum, suggesting increased sensitivity to metoprolol during pregnancy (58). Labetalol is discussed later in the text.

TABLE 2 Medications Used in Pregnancy for CVD

Drug Name	Former FDA Category*	Adverse Effects and Other Comments	Placental Transfer	Transfer to Breast Milk
Adenosine	C	Dyspnea, bradycardia. Endogenous substance with short half-life; may require increased dosages in pregnancy.	No.	Unknown, endogenous to breast milk.
Amiodarone	D	Congenital goiter, thyroid disorders (hypothyroidism), QT prolongation, neurodevelopmental abnormalities and premature birth. Use only after other antiarrhythmics have failed, prolonged half-life, fetal effects unrelated to duration of use or dose.	Yes.	Yes. Due to prolonged half-life, manufacturer recommends discontinuation of nursing if drug use is needed.
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprysilin inhibitor, direct renin inhibitors	X	Oligohydramnios, IUGR, decreased fetal renal function, lung hypoplasia and skeletal malformations. Contraindicated in pregnancy.	Yes.	Yes. Captopril, benazepril, and enalapril may be considered in the postpartum period with close follow-up of the child's weight initially. Manufacturers recommend against use of other agents during lactation.
β-blockers Labetalol Atenolol Metoprolol Carvedilol	C (atenolol D)	Bradycardia, hypoglycemia, reduced birth weight. Labetalol used for HTN (first line), requires dose changes with GA and lean-weight. Atenolol associated with significant IUGR.	Yes.	Yes. Labetalol—safe (reported asymptomatic bradycardia and Raynaud phenomenon). Metoprolol—acceptable, no adverse effects reported in a small trial. Carvedilol—unknown.
Calcium channel blockers Nifedipine Verapamil Diltiazem Amlodipine	C	Pre-maturity, IUGR, fetal bradycardia in some CCB, suspected neonatal seizures if used in third trimester. Nifedipine used as HTN (first line) and tocolysis (may create maternal hypotension and fetal hypoxemia when used with magnesium). Verapamil, along with β-blockers, is preferred for paroxysmal SVT compared to diltiazem. Diltiazem is associated with adverse fetal effect in animal studies. Amlodipine is probably safe for HTN.	Yes (no for diltiazem).	Yes. Minimal exposure. Nifedipine is considered safe, but there is little data about verapamil and diltiazem.
Cholestyramine resin/colestipol	C	May lower fat-soluble vitamins.	Unknown.	No. May be used during lactation but may interfere with maternal vitamin levels.
Clonidine	C	May require shortening dosage intervals; may be used in a transdermal preparation for patients who cannot tolerate oral medications.	Yes.	Yes.
Digoxin	C	Low birth weight. Used as first line for symptomatic SVT using the lowest effective dose; serum levels are unreliable throughout pregnancy. Used as fetal AAD.	Yes.	Yes. Minimal exposure.
Disopyramide	C	Uterine contraction, placental abruption, prolonged QT.	Yes.	Yes.
Diuretic agents Loop diuretic agents (e.g., furosemide) Thiazides (e.g., HCTZ, metolazone) Spironolactone/eplerenone	C (eplerenone B)	Oligohydramnios, fetal electrolyte abnormalities. Furosemide commonly used for edema and HF, might be associated with increased birth weight. Limited data about torsemide and bumetanide. HCTZ used for HTN if used before pregnancy, not recommended for routine diuretic purposes. May be associated with fetal/neonatal jaundice, thrombocytopenia, and maternal bleeding diathesis and hyponatremia. Spironolactone has anti-androgenic (feminization) effect during first trimester. Eplerenone had adverse effects in animal reproduction studies.	Yes.	Yes. Diuretics can suppress lactation. Both furosemide and HCTZ are acceptable, yet require infant follow-up. Limited data on other diuretics. Spironolactone and eplerenone are not recommended for lactation.
Dopamine	C	Cardiac resuscitation drugs are used similarly to nonpregnancy state. May have vasoactive effect on fetus, animal reproduction studies had shown adverse effects.	Unknown.	Unknown.
Dobutamine	B	Cardiac resuscitation drugs are used similarly to nonpregnancy state. Not to be used in stress testing during pregnancy.	Unknown.	Unknown.
Endothelin-receptor antagonists (bosentan, ambrisentan, macitentan)	X	Associated with birth defects including mandibular malformations and cardiac defects.	Unknown.	Limited data.
Epinephrine	C	Cardiac resuscitation drugs are used similarly to nonpregnancy state. May cause uterine vasoconstriction and fetal hypoxia. Also used for anaphylaxis and severe asthma.	Yes.	Unknown.
Ezetemibe		Associated with adverse fetal effect in animal studies. Not recommended.	Unknown.	Unknown.
Fenofibrate	C	Limited data. Not recommended.	Yes.	Unknown.

Continued on the next page

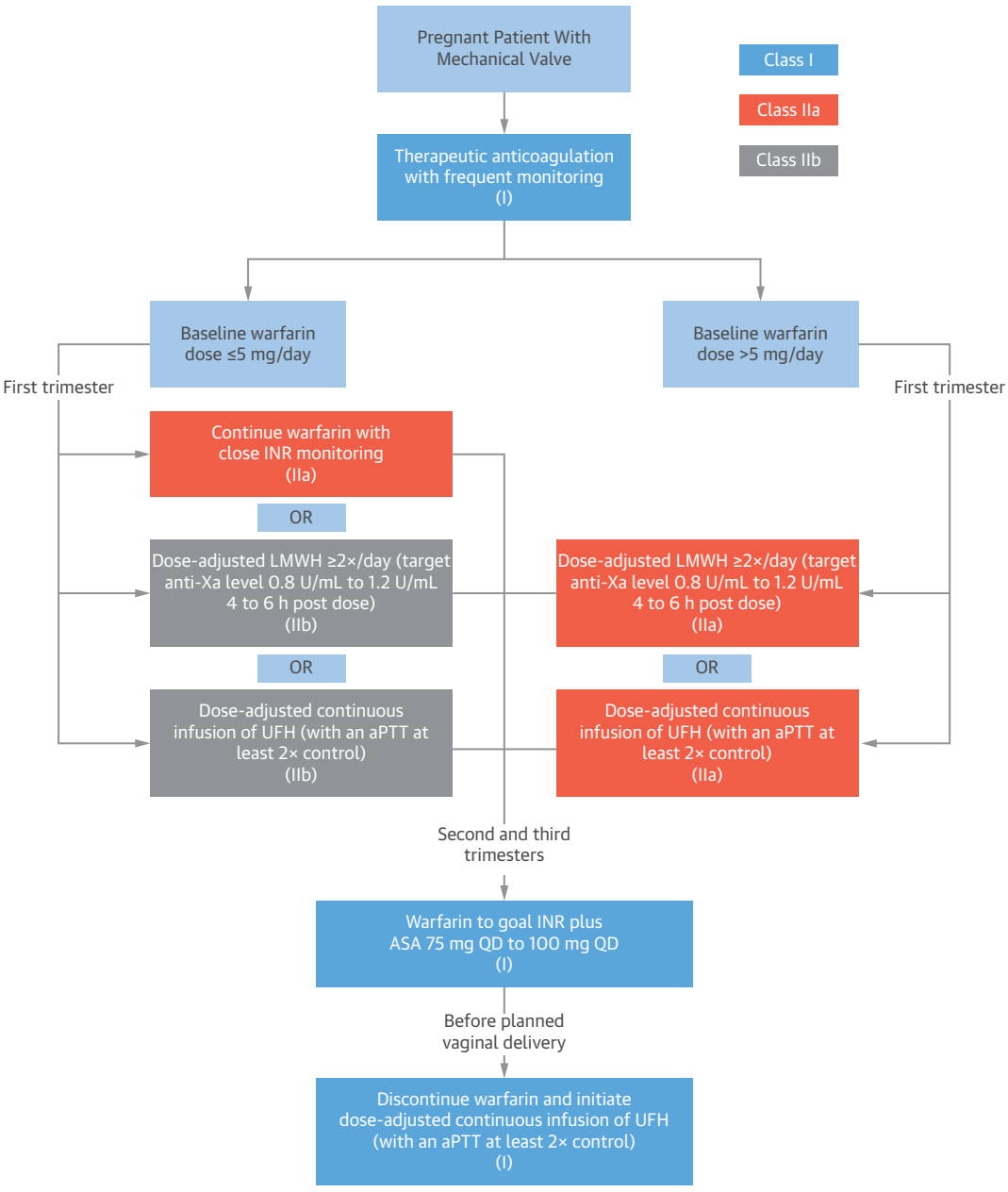
TABLE 2 Continued

Drug Name	Former FDA Category*	Adverse Effects and Other Comments	Placental Transfer	Transfer to Breast Milk
Flecainide	C	Maternal visual disturbances, acute interstitial nephritis, obstetric cholestasis, fetal bradycardia. Used for maternal and fetal AAD.	Yes.	Yes.
Fondaparinux	B	Used in allergies to heparin and heparin-induced thrombocytopenia.	Yes.	Unknown.
Gemfibrozil	C	Associated with adverse fetal effect in animal studies. Not recommended.	Yes.	Unknown.
Heparins UFH LMWH—enoxaparin	C—UFH B—enoxaparin	Meticulous monitoring needed for anticoagulation in women with mechanical valves. Heparin-induced thrombocytopenia (heparin >LMWH), osteoporosis.	No.	Unknown.
Hydralazine	C	Lupus-like syndrome, reflex tachycardia, fetal thrombocytopenia. Used for HTN and HF.	Yes.	Yes.
Ibutilide	—	Limited data.	Unknown.	Unknown.
Iloprost	C	Limited data.	Unknown.	Unknown.
Isosorbide dinitrate	B	Animal reproduction studies have shown adverse effects.	Unknown.	Unknown.
Ivabradine	—	Animal reproduction studies have shown adverse effects.	Yes (in rats).	Unknown.
Levosimendan	—	Vasodilator for the management of HF (especially in the setting of PPCM), not available in the United States.	Unknown.	Unknown.
Lidocaine	B	CNS depression, cardiac and vascular tone effects. Limited data for use in ventricular arrhythmias, but can be considered.	Yes.	Yes.
Methyldopa	B/C (injectable)	Used for HTN (first line). 1% liver toxicity.	Yes.	Yes.
Mexiletine	C	Used for ventricular arrhythmia. Limited data, but probably safe.	Yes.	Yes.
Milrinone	C	Cardiac resuscitation drugs are used similarly to nonpregnancy state. Increased resorption during pregnancy reported.	Unknown.	Unknown.
Nitroglycerin	C	Used for HF, HTN, and uterine relaxation.	Unknown.	Unknown.
Nitroprusside	C	Fetal cyanide and thiocyanate toxicity.	Yes.	Yes (metabolites).
Norepinephrine	C	Cardiac resuscitation drugs are used similarly to nonpregnancy state.	Yes.	Unknown.
PDE-5i (sildenafil, tadalafil)	B	Limited data.	Unknown.	Yes.
Platelet aggregation inhibitors Aspirin Clopidogrel Prasugrel Ticagrelor	N—aspirin B—clopidogrel C—ticagrelor —prasugrel	Aspirin is associated with IUGR, fetal bleeding, and neonatal acidosis. High dose aspirin is associated with premature closure of PDA. Other antiplatelets are not well studied.	Yes (aspirin). Unknown—clopidogrel, ticagrelor, prasugrel.	Aspirin: transfers but might be safe at low dose (manufacturer recommends against use). Clopidogrel: unknown. Prasugrel and ticagrelor: transferred in rat studies.
Procainamide	C	Lupus-like syndrome, prolonged QT.	Yes.	Yes.
Propafenone	C	Limited data. Probably safe	Yes.	Yes.
Quinidine	C	Fetal thrombocytopenia, prolonged QT.	Yes.	Yes.
Sotalol	B	Higher risk for TdP (prolonged QT), fetal bradycardia, hypoglycemia, reduced birth-weight. Increasingly used for fetal atrial flutter.	Yes.	Yes.
Statins	X	Limited data, congenital anomalies.	Yes.	Unknown.
Thrombolytics Alteplase Streptokinase	C	Relative contraindication in pregnancy and peripartum. Should not be withheld in a life-threatening event. Adverse effects in animal studies with alteplase. Increased risk of bleeding (primarily genital), fetal loss (6%), preterm birth (6%).	Minimal.	Unknown.
Treprostinil	B	Limited data, adverse effects shown in animal studies.	Unknown.	Unknown.
Warfarin	X	Crosses placenta, risk of embryopathy in first trimester (nasal and limb hypoplasia, stippled epiphyses), CNS abnormalities, and hemorrhage remains throughout pregnancy. Risk of embryopathy is decreased with daily dose ≤5 mg. Primary indication is mechanical valves.	Yes.	Minimal transfer, if any. Monitor for infant bruising.

*Categories: A) no demonstrated risk to the fetus based on well-controlled human studies; B) no demonstrated risk to the fetus based on animal studies; C) animal studies have demonstrated fetal adverse effects, no human studies, potential benefits may warrant use of the drug; D) demonstrated human fetal risk, potential benefits may warrant use of the drug; and X) demonstrated high risk for human fetal abnormalities outweighing potential benefit; N) nonclassified.

AAD = antiarrhythmic drug; ACLS = advanced cardiac life support; CNS = central nervous system; FDA = Food and Drug Administration; GA = gestation age; HCM = hypertrophic cardiomyopathy; HCTZ = hydrochlorothiazide; HF = heart failure; HTN = hypertension; IUGR = intrauterine growth restriction; LMWH = low molecular weight heparin; PDE-5i = phosphodiesterase 5 inhibitor; SVT = supraventricular tachycardia; TdP = torsades de pointes; UFH = unfractionated heparin.

FIGURE 2 Anticoagulation of Pregnant Patients With Mechanical Valves



aPTT = activated partial thromboplastin time; ASA = aspirin; INR = international normalized ratio; LMWH = low molecular weight heparin; QD = once daily; UFH = unfractionated heparin. Adapted from Nishimura et al. (143).

CALCIUM CHANNEL BLOCKERS. In 2011, a study by Davis et al. (59) found an increased risk of neonatal seizures in infants exposed to calcium channel blockers (CCB) compared with unexposed infants, primarily in the third trimester, suspected to be related to hypocalcemia. However, later largescale studies did not reproduce the finding (60,61).

Verapamil can be used for short- and long-term treatment of maternal SVT as well as fascicular VT (1,62). Verapamil has not been associated with adverse effects to the fetus, yet has been associated with maternal hypotension (63,64). Verapamil undergoes extensive first-pass metabolism with only 22% reaching circulation unaltered in normal subjects (65,66).

There is a single case report of congenital hypertrophic cardiomyopathy occurring with verapamil exposure, which has also been shown in rats (67).

Diltiazem is used both for maternal arrhythmias and as an agent to promote tocolysis in preterm labor (68), and may decrease proteinuria (69). In animal studies, diltiazem can result in decreased fetal weight and skeletal abnormalities (70). Diltiazem levels in breastmilk closely follow the maternal serum concentration, and can reach approximately the same peak level as in the serum (65,71). Nifedipine is discussed later in the text.

Digoxin has a long record of well-tolerated use for maternal and fetal SVT. The pharmacokinetics are complex, with pregnancy physiology resulting in changes to normal bioavailability and clearance (72). In a study of 10 pregnant women given metildigoxin, there was a significant increase in drug clearance in pregnant women compared with nonpregnant women (183 ml/min vs. 140 ml/min; $p < 0.001$) (73). In a group where digoxin was used as a model substrate to study P-glycoprotein transport activity, 14 pregnant subjects at approximately 30 weeks were used as their own controls in the postpartum period. The authors found that women in the third trimester had an increased unbound fraction of digoxin and increased renal clearance (61%) of digoxin compared with the postpartum period (74). The common net effect of these 2 opposing processes is reduced drug effect of digoxin during pregnancy.

The assay for measuring digoxin may be compromised in pregnant women, who have circulating digoxin-like fragments that can falsely elevate levels (75). Higher digoxin levels in pregnant women should not, however, exclude toxicity when the level is normal. Clinicians should look for clinical signs of digoxin toxicity at any level, such as arrhythmia (76) and vomiting. Though there is a report of intrauterine digoxin toxicity after maternal overdose, the neonate actually tolerates higher digoxin doses well when their exposure dose is adjusted for body surface area (77).

Flecainide is mainly used in pregnancy for maternal and fetal SVT, maternal idiopathic sustained VT, and long-term management of SVT (1). Flecainide has also been used in severe arrhythmogenic right ventricular (RV) cardiomyopathy and sustained polymorphic VT cases, both with good neonatal outcomes (78,79). Flecainide is increasingly being recognized as an effective option for the treatment of fetal SVT (80,81). Flecainide for fetal SVT was first described in 1988 by Wren et al. (82) when a hydropic fetus was converted with intravenous flecainide after digoxin had failed. Subsequent early cases used oral flecainide either after digoxin failure or as initial therapy (83). Multiple studies show improved fetal outcomes with flecainide compared with digoxin or in combination therapy with digoxin for fetal SVT, especially in hydrops fetalis with 3 days as the median time to normal sinus rhythm and a trend toward reduced mortality (84,85). Adverse events noted in flecainide trials and reports include maternal visual disturbance, prolongation of maternal QT interval corrected for heart rate (QTc), prolonged neonatal QT intervals and heart failure at toxic levels, cholestasis of pregnancy, and decreased fetal heart rate variability.

Little is known about propafenone's safety in pregnant women, and it has not been studied during organogenesis (86). Propafenone was used without harmful effects in the fetus in cases of arrhythmogenic RV dysplasia (87), WPW (88), and structural-related premature ventricular contractions (89).

VENTRICULAR ARRHYTHMIAS IN PREGNANCY. VT or fibrillation arising during pregnancy suggests underlying cardiac structural abnormalities. The development of new VT late in pregnancy in an otherwise normal heart should prompt an investigation for peripartum cardiomyopathy (PPCM). Unstable patients should undergo electric cardioversion. Hemodynamically stable women can be treated with electric cardioversion or with lidocaine or β-blockers. ESC guidelines also recommend procainamide, flecainide, and sotalol (1). Amiodarone is to be used if all other measures fail. β-Blockers are the mainstay treatment for suppressive therapy for VT.

Lidocaine has been better studied as an anesthetic than as an antiarrhythmic agent, and the available pharmacokinetic data coming from studies of its use as an anesthetic suggest the agent is safe. Sixty-to-seventy percent of lidocaine is protein-bound, and it rapidly enters maternal circulation and crosses the placenta even after epidural administration (65). There have been 2 published cases of lidocaine being used for ventricular arrhythmia during labor and delivery, even through the epidural catheter (90,91). CNS depression may be an adverse effect at high doses.

Mexiletine is a lipid-soluble oral and has limited data in pregnancy, but appears safe (92).

Quinidine, historically used for malaria treatment, has been used to treat both maternal atrial and ventricular tachyarrhythmias since the early twentieth century. It has also been used along with isoproterenol to treat a pregnant woman with Brugada syndrome and recurrent VT (93). Adverse effects include increased possible fetal cranial nerve VIII damage, uterine contractions, neonatal thrombocytopenia, and QT prolongation (1).

Procainamide is more commonly used in the modern era than quinidine for long-term management of

SVT or for short-term conversion of hemodynamically stable monomorphic VT and occasionally for fetal SVT (94). It is associated with maternal lupus-like syndrome and QT prolongation.

Amiodarone should only be used for maternal SVT as a last-line agent if other agents have failed (1). Amiodarone is a highly lipophilic drug that accumulates in skeletal smooth muscle and adipose tissue (95). Its half-life lasts for weeks to months. Amiodarone, its metabolite desethylamiodarone, and iodine are all capable of transplacental transfer. Great caution should be exercised in the use of amiodarone, whose adverse effects on the fetus appear unrelated to duration or total dose of treatment (96). The most worrisome side effects are thyroid dysfunction, especially neonatal hypothyroidism, and neurodevelopmental abnormalities. It is unknown whether the toxic effects are directly from the drug itself or from induction of thyroid dysfunction. Neonatal thyroid tissue may be unable to escape the Wolff-Chaikoff effect (where increased iodine suppresses thyroid hormone production) in the same way that adult tissue can, and therefore fetuses may be more susceptible to adverse effects of amiodarone's iodine load (97). Neonatal hypothyroidism is usually transient with incidence reported at 17% to 25% in mothers who received amiodarone (96-99). Hyperthyroidism is less common but also recorded in the fetus, and thyrotoxicosis may be more pronounced in iodine-deficient countries (97).

Although neonatal hypothyroidism is frequently transient and does not usually result in goiter, there may still be lasting neurodevelopmental adverse effects. There are cases of fetal hypothyroidism but normal neurodevelopmental outcomes (99,100), normal thyroid with abnormal neurodevelopment (97,101), and cases where both exist (96). The effects are not linked to trimester when administered, and there are several cases of normal neonatal outcomes even when amiodarone was started before pregnancy (102,103). Other adverse effects to look for include bradycardia and QT prolongation in infants.

Sotalol is an AAD with one of the greatest risks of torsades de pointes due to QT interval prolongation. Its use in pregnancy is mainly in management of fetal arrhythmias, recommended primarily for atrial flutter and VT (104). Maternal QTc should be monitored closely when sotalol is used.

MEDICATIONS USED FOR TREATMENT OF HYPERTENSION AND HEART FAILURE

HYPERTENSION. Hypertension complicates 5% to 10% of pregnancies and is associated with obstetric and fetal complications as well as increased future risk of cardiovascular disease (1,105). The major hypertensive disorders of pregnancy include pre-existing or chronic hypertension (hypertension diagnosed before 20 weeks of gestation), gestational hypertension (diagnosed after 20 weeks of gestation), pre-existing hypertension with superimposed gestational hypertension with proteinuria, and pre-eclampsia. Hypertension during pregnancy is defined as blood pressure ≥140/90 mm Hg on 2 separate readings; severe hypertension is defined as ≥160/110. Guidelines vary with respect to target blood pressure goals for each treatment group. The ESC recommends drug treatment in all pregnant women with values above 150/90 mm Hg, and ≥140/90 in women with gestational hypertension, pre-existing hypertension with superimposed gestation hypertension, or hypertension with subclinical organ damage or symptoms. The American Congress of Obstetricians and Gynecologists (ACOG) recommends therapy for gestational hypertension and preeclampsia without end-organ damage for values exceeding 160/105 mm Hg. For pregnant women with chronic hypertension on therapy, ACOG recommends a goal range of 120 to 160 mm Hg systolic and 80 to 105 mm Hg diastolic with stricter control in the setting of end-organ damage (106,107). Unfortunately, the use of antihypertensive agents in pregnancy has not been shown to reduce the risk of preeclampsia (108), nor tighter control (diastolic pressure <85 mm Hg) to reduce obstetric or fetal complications (109,110). Of note, the placenta does not autoregulate blood flow, and therefore, acute maternal hypotension secondary to antihypertensive treatment may cause fetal distress manifesting initially with fetal heart rate decelerations (111).

First-line antihypertensive agents for chronic and gestational hypertension include oral labetalol, nifedipine, and methyldopa (1). Second line may include other β-blockers (excluding atenolol) and other CCB (112). Therapies may need a dose reduction in the second trimester due to a 5 to 10 mm Hg physiological decrease in the mean blood pressure values. ACE inhibitors, angiotensin receptor blockers (ARBs), direct renin-inhibitors, angiotensin receptor-neprysilin inhibitor (ARNi), spironolactone, and eplerenone are contraindicated in pregnancy and are discussed later in the text. Women with chronic hypertension can continue their pre-pregnancy drugs unless contraindicated. Caution is advised with long-term use of diuretic agents in pregnancy due to concerns for a decrease in placental perfusion, especially in the setting of preeclampsia.

Therapy for hypertensive emergencies (>160 to 180/110 mm Hg) includes intravenous therapies such

as labetolol or hydralazine and oral nifedipine or alpha-methyldopa (AMD) (1,110). In the updated ESC guidelines, hydralazine is no longer the drug of choice due to its adverse effect profile (see later in the text). Nitroglycerin is recommended for hypertension with pulmonary congestion and preeclampsia. Sodium nitroprusside should only be used in refractory cases of hypertension due to the potential for cyanide toxicity.

Labetalol is a nonselective α, β-1, and β-2 receptor blocker that is used as first line for both acute and chronic hypertension in pregnancy. Dose adjustment along the course of the pregnancy may be required due to increasing clearance leading to a shorter half-life (110). In a study of 57 pregnant women who received oral labetalol for hypertension, subjects at week 12 had 1.4 times the clearance of postpartum subjects, and at week 40 had 1.6 times the clearance of postpartum subjects (113). Documented fetal effects include hypoglycemia, bradycardia, hypotension, and respiratory depression, as well as IUGR. However, labetalol is considered safe with no fetal malformations profile and has similar outcome data to nifedipine and AMD (106).

Nifedipine is another safe first-line drug used for both blood pressure control and tocolysis (114). It may require shorter dosing intervals or higher dosages due to accelerated liver metabolism during pregnancy through CYP3A4. No increase in teratogenicity has been observed with nifedipine. However, in the APOSTEL III (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour) trial, which compared nifedipine to atosiban, an oxytocin inhibitor used for tocolysis, both agents exhibited similar perinatal events as the primary outcome, yet nifedipine had a nonsignificant increase in neonatal mortality (5% vs. 2%) (115). Hypotension may develop with concomitant use of magnesium. Concerns for neonatal seizures or postpartum hemorrhage have been dismissed by large cohort studies (59,60,116).

Alpha methyl dopa (AMD) is an α-2 adrenergic receptor agonist that decreases brain sympathetic activity. It is considered a first-line agent for hypertension in pregnancy, although infrequently used nowadays and probably less effective compared with β-blockers or CCB. AMD does not require any dose adjustment in pregnancy. No obvious teratogenic effects have been observed in animal studies; however, in a study following 92 patients for 7.5 years after delivery, head circumference in male children was smaller (117). Hepatotoxicity is an important adverse effect that has been observed in 1% of pregnant patients using AMD. It is dose related and may progress to fulminant hepatitis (118).

Hydralazine, an arterial vasodilator, is used for the treatment of acute-onset and severe hypertension as well as heart failure during pregnancy and may be used orally or intravenously (119). Oral hydralazine in patients with preeclampsia was shown to have no effect on placental perfusion (120). Hydralazine is associated with reflex tachycardia, maternal lupus-like symptoms, and fetal thrombocytopenia. Compared with labetalol and nifedipine, there may be increased maternal and fetal complications, and therefore it is no longer considered first-line therapy (1,121).

Clonidine is an α-2 agonist which has similar hypotensive effects in pregnancy as AMD (122). The pharmacokinetics show higher nonrenal clearance during gestation that may require shorter dosing intervals (123). Abrupt cessation of the drug may result in rebound hypertension. Clonidine crosses the placenta, and animal studies did show adverse effects. Its formulation as a transdermal patch may be advantageous for patients who cannot tolerate oral medications.

DIURETIC AGENTS. Indications for diuretic therapy during pregnancy include hypertension, hypervolemia, or heart failure management. The major concerns of diuretic agents are related to reduction in plasma volume, cardiac output, and decrease in uterofetal perfusion.

Furosemide, the most commonly used diuretic agent in pregnancy, has been associated with neonatal jaundice, thrombocytopenia, maternal pancreatitis, and hyponatremia. However, in a large meta-analysis, there was no significant difference in adverse effects compared with pregnant patients not using diuretics. Furosemide was also associated with higher birth weight infants (mean increase of 104.7 g compared with the nondiuretic group), although the authors argued that the finding may have been related to referral bias and not a diabetogenic effect caused by the drug (124).

Hydrochlorothiazide (HCTZ) is primarily continued during pregnancy, rather than initiated. It has been associated with lower birth weights (125), neonatal jaundice, thrombocytopenia, and bleeding diathesis. No teratogenic effects have been reported (106).

ACE INHIBITORS, ARBs, DIRECT RENIN-INHIBITORS, ARNi, AND ALDOSTERONE ANTAGONISTS. ACE inhibitors, ARBs, direct renin-inhibitors are category X, are contraindicated in pregnancy, and should be withheld in the pre-conception period. These medications were shown to cause renal dysgenesis, oligohydramnios as a result of fetal oliguria, calvarial and pulmonary hypoplasia, IUGR, and neonatal anuric renal failure, resulting in fetal death particularly if

used in the second and third trimester (126). However, during lactation, benazepril, captopril, and enalapril may be safely considered. There are no data on ARB and ARNi during lactation, and therefore, they should not be used. Aldosterone antagonists, spironolactone and eplerenone, are contraindicated in pregnancy due to their antiandrogen effects on the male fetus in the first trimester and evidence of teratogenesis in a rat model. They are also contraindicated during lactation.

CARDIOMYOPATHIES AND HEART FAILURE. Cardiomyopathies during pregnancy may be inherited (e.g., dilated) or acquired (e.g., PPCM, viral, stress-induced, or toxic). Pregnancy portends a high rate of maternal and fetal complications and is contraindicated in women with systolic dysfunction beyond the mild range (left ventricular ejection fraction <40%). ACE inhibitors, ARBs, direct renin-inhibitors, aldosterone antagonists, and ivabradine are contraindicated and should be stopped before pregnancy or in cases where the woman was found to be pregnant (1,127). β-1 selective blockers, such as metoprolol succinate, are favored as to avoid interfering with β-2-mediated uterine relaxation and peripheral vasodilation. Carvedilol, an α/β-adrenergic blocker, has not been shown not to be associated with growth restriction (128). Before pregnancy, it is advisable to attempt a trial period of several months without the contraindicated agents, with close observation of symptoms and imaging of systolic function to ensure no clinical deterioration.

Management of acute heart failure and cardiogenic shock in pregnancy is based on current heart failure guidelines (1). Urgent delivery is recommended in severe cases and cardiogenic shock. Diuretics such as furosemide, bumetanide, and HCTZ are used for symptomatic pulmonary edema and, as mentioned before, hold the risk of decreasing placental perfusion and causing an electrolyte imbalance in the fetus. For afterload reduction, hydralazine plus nitrates are used in place of ACE inhibitors and ARBs. After initial stabilization, β-blockers should be initiated and digoxin can be considered. Postpartum, neurohormonal blockade can be restarted (1).

Paucity of data and lack of guidelines exist in regard to inotrope and vasopressor use for the critically ill pregnant patient. For inotrope support, dopamine and dobutamine have been safely used in pregnancy (119). Levosimendan, a calcium sensitizer, is recommended in the setting of PPCM as dobutamine may be associated with heart failure progression in these patients (129). Vasopressors carry the risk of reducing uterine blood flow, although norepinephrine, commonly used as the first-line vasoactive agent, has not been shown to affect the fetus (130).

Bromocriptine increases cleavage of prolactin to a 16-kDa prolactin subfragment isoform thereby promoting apoptosis and inflammation while suppressing angiogenesis. It has demonstrated positive results with improvement of ventricular function in women with PPCM; however, larger randomized-controlled trials are needed for validation (131). Anticoagulation should be administered in patients with PPCM receiving bromocriptine (1).

Heart transplantation recipients may undergo pregnancy after comprehensive pre-gestational counseling and stratification of their risk of rejection, infection, graft failure, and teratogenicity of the immunosuppressive therapy. The most common complications encountered during pregnancy are hypertension, thromboembolic disease, and hyperemesis. The altered hemodynamics and volume changes during pregnancy also affect the levels of the immunosuppressive medications and require close monitoring. Corticosteroids and calcineurin inhibitors (e.g., cyclosporine, tacrolimus) and azathioprine can be continued during pregnancy, whereas mycophenolate mofetil should be discontinued (132). Breastfeeding is contraindicated.

VALVULAR HEART DISEASE

The specific management of valvular disease during pregnancy is beyond the scope of this paper. Stenotic lesions such as mitral or aortic stenosis are far less tolerated during pregnancy as compared with regurgitant lesions. Particular attention should be paid to the hemodynamic effects of stenotic lesions in the early postpartum period. Medical therapy primarily consists of diuretic therapy for congestive states and, in the case of mitral stenosis, beta-blockade to allow more ventricular filling and anticoagulation in the setting of AF, left atrial thrombus, or prior embolism (1). Catheter-based interventions or surgery are needed in severe hemodynamic decompensation. Mechanical prosthetic valves are discussed later in the text.

ISCHEMIC HEART DISEASE

Coronary artery dissection is the most common cause of ischemic heart disease in pregnancy (133). Other mechanisms of ischemia include spasm, prior Kawasaki disease, atherosclerotic disease with increased maternal age and CVD risk factors, and toxins such as cocaine. Presentation is more common in the third trimester or postpartum period, and the majority of cases are coronary dissection, thrombus or embolic

event (134,135). Initial treatment of acute myocardial infarction in pregnancy is identical to the nonpregnant state. Percutaneous coronary intervention is preferable to fibrinolysis. Unstable angina therapy includes antiplatelet therapies (see later in the text), β-blockers or CCB, heparin or low molecular weight heparin (LMWH), and nitrates. Bivalirudin and glycoprotein IIb/IIIa inhibitors are not recommended due to lack of data (1).

STATINS AND OTHER LIPID-LOWERING THERAPIES DURING PREGNANCY

The data on use of statins, hydroxymethyl glutaryl coenzyme A reductase inhibitors, is mixed. Although case reports and retrospective reviews previously suggested a link to teratogenic effects, in a multicenter, observational prospective trial with pregnant women exposed to statins in the first trimester, there was no significant increase in the rate of major birth defects. However, premature birth was more frequent (136). In a more recent systemic review, there was no clear relationship with statin use in pregnancy and congenital anomalies. The authors concluded that statins are probably not teratogenic; however, given the limited data and quality of the information, statins are to be avoided during pregnancy (137). Statins remain contraindicated for use in pregnancy and should be discontinued before conception (138,139).

Bile acid sequestrants (i.e., cholestyramine and colestipol) inhibit absorption of lipids at the gut level and are considered safer than other lipid-lowering agents, and are the treatment of choice for hyperlipidemia. However, they also lower absorption of fat-soluble vitamins, which may affect the fetus (140). Other lipid-lowering agents with potential teratogenic effects include gemfibrozil, fenofibrate, and ezetimibe.

ANTIPLATELET AND ANTICOAGULATION THERAPY

Pregnancy is associated with a hypercoagulable state due to enhanced production of certain clotting factors, decrease in protein S activity, and inhibition of fibrinolysis (141). Thrombotic complications are a major cause of maternal morbidity and mortality (142). The risk of thromboembolic complications is increased throughout pregnancy, peaks at the first week postpartum, and remains elevated for the first 6 weeks postpartum. Anticoagulation therapy during pregnancy is indicated for prevention or treatment of venous thromboembolism, inherited thrombophilia, anti-phospholipid antibody syndrome, IUGR, and mechanical heart valves.

ANTICOAGULANTS. Warfarin is a vitamin K antagonist (VKA) that crosses the placenta. The American Heart Association/American College of Cardiology guideline recommendations for use of VKAs during pregnancy were revised in 2014 in recognition of the dose-dependent relationship with increased adverse outcomes (143). The rates of embryopathy, miscarriage, and stillbirth occur with increased frequency with daily doses >5 mg (144). Women with mechanical heart valves are at risk during pregnancy for valve thrombosis and hemorrhagic complications, and anticoagulation must be meticulously monitored. Guidelines recommend that women taking >5 mg of VKA during the first trimester should be switched to LMWH or unfractionated heparin by the end of the sixth week of gestation to decrease the risk of embryopathy. The American Heart Association/American College of Cardiology guidelines include an anticoagulation management algorithm of women with mechanical heart valves during pregnancy (**Figure 2**) (143). Fetal warfarin syndrome or "Di Sala syndrome" primarily affects the fetus in the first trimester because warfarin crosses the placenta. It is associated with facial dysmorphism such as nasal hypoplasia, skeletal abnormalities (limb hypoplasia and stippled epiphyses), central nervous system abnormalities (ventral and dorsal midline dysplasia), and cardiac defects (145-147). Second and third trimester effects include a ~1% incidence of ocular and central nervous system abnormalities as well as intracranial hemorrhage (1). Women who receive VKA throughout pregnancy should be changed to either LMWH or unfractionated heparin at 36 weeks' gestation in order to reduce the risk of fetal hemorrhage at the time of vaginal delivery and delivery-associated maternal bleeding (148). Women who are using LMWH are not candidates for regional anesthesia within 24 h of their last dose, so a timed delivery is helpful to prevent complications of bleeding from long-acting injectable anticoagulants. Reversal of VKA in the mother does not ensure reversal in the fetus, thus if a patient presents in labor while on a VKA, a cesarean delivery should be performed to prevent fetal intraventricular hemorrhage during passage through the birth canal.

LMWH does not cross the placenta, and peak and trough anti-Xa levels must be followed meticulously during pregnancy. Women are often at greatest risk of mechanical heart valve complications during the time of transition from VKA to heparin (149). Mechanical valve thrombosis has been reported in 4.7% of pregnant women with mechanical valves (149). In a recent meta-analysis of maternal and fetal outcomes in over 800 women with mechanical heart valves on different

anticoagulant strategies, Steinberg et al. (150) confirmed that VKA 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.

Alternative anticoagulant strategies may be utilized in select cases. Fondaparinux is an indirect Factor Xa inhibitor and is recommended by the ACOG in the setting of heparin-induced thrombocytopenia or heparin allergy (151). At this time, there is insufficient data to recommend bivalirudin or the direct oral anticoagulants for women in pregnancy.

ANTIPLATELET AGENTS. Low-dose aspirin (75 to 100 mg) is commonly used in the prevention of preeclampsia. It is also recommended in the second and third trimesters for women with mechanical or bioprosthetic valve prostheses (143). However, given increased risk of bleeding when used in combination with other anticoagulants, new ESC guidelines do not recommend use of low-dose aspirin for mechanical valves, in contrast to the AHA/ACC guidelines (1,143). There is no evidence that low-dose aspirin increases maternal or fetal bleeding risks, risk of placental abruption, congenital anomalies, or complications at the time of neuraxial anesthesia during delivery (152,153). High-dose aspirin should be avoided in pregnant women, due to the risk of premature closure of the ductus arteriosus.

Clopidogrel inhibits platelet aggregation and activation by preventing binding of fibrinogen to the adenosine diphosphate receptor. Animal studies demonstrate no adverse pregnancy effects with limited human data (154). It may be used in pregnancy for the shortest duration possible (1). Before neuroaxial anesthesia, it must be discontinued for 7 days to decrease the risk of epidural hematoma (155). There are little data in regard to prasugrel, ticagrelor, abciximab, or eptifibatide, and their use is not recommended (156).

ADVANCED THERAPIES FOR PULMONARY HYPERTENSION

The dramatic hemodynamic changes of pregnancy may exacerbate right heart failure, increase right-to-left shunting in cyanotic patients, and have fatal consequences for women with pulmonary hypertension (PH). Multiple guideline and consensus documents advise that women with PH, particularly type 1 pulmonary arterial hypertension, should be counseled against pregnancy (1,157). Historical reports of pregnant women with PH report very poor survival, with fatality rates often exceeding 50% in small case series (158). However, as the medical therapies for PH have developed, there has been some progress made in the management of women with PH during pregnancy, resulting in improved, yet still guarded, outcomes. A recent publication from the ROPAC registry reported improved outcomes in a group of 151 women with PH. No deaths occurred during pregnancy, 3.3% of women died in the first week postpartum, and an additional 2.6% died within 6 months of delivery (159). However, this registry includes women diagnosed with milder forms of PH, and >50% of the women included were based on echocardiographic data alone. In fact, 3 of the 7 women (43%) with idiopathic PH died. Only 9 women in this registry were on advanced PH medications, emphasizing that these registry data may reflect women with less advanced forms of PH.

In 2015, the Pulmonary Vascular Research Institute published a statement on pregnancy and PH with consensus-based recommendations for management (160). These recommendations include the use of parenteral prostaglandins (intravenous epoprostenol, treprostinil) in women with World Health Organization (WHO) functional class (FC) IV or significant RV dysfunction. Epoprostenol (161) has been the most extensively studied. The drugs may affect platelet aggregation and promote bleeding.

Inhaled prostaglandins, such as iloprost (162,163), may be considered in select women with more preserved RV function that are in WHO FC III. In woman with normal RV function, who are in FC I or II, oral phosphodiesterase 5 inhibitors (sildenafil or tadalafil) may be considered (164). Additionally, there have been reports of successful pregnancies using a combination therapy of epoprostenol and sildenafil (165).

For women who have vasodilator-responsive pulmonary artery hypertension and who have preserved RV function, it may be reasonable to continue CCB therapy during pregnancy. Patients on anticoagulation may also continue therapy throughout pregnancy. Lastly, endothelin receptor blockers (e.g., bosentan, ambrisentan, macitentan) should not be used in pregnancy due to the teratogenic potential (e.g., mandibular malformation, cardiac defects).

CONNECTIVE TISSUE DISEASES

Some women with Marfan syndrome (MFS) experience further aortic root dilatation with a higher risk of dissection during pregnancy (166). Other high-risk aortic syndromes include Loeys-Dietz, Ehlers-Danlos type IV (vascular type), and osteoaneurysm syndrome. Turner syndrome women who commonly have bicuspid aortic valves (BAV), coarctation of the aorta, hypertension, and other cardiovascular risk

factors, are now able to become pregnant through means of assisted reproduction, which places them at particularly higher risk of aortic events (167). Nonsyndromic BAV is a risk factor for dissection during pregnancy, but reportedly less than MFS (168). MFS and other high-risk patients should have a comprehensive pre-conception workup, and women who are taking β-blockers for the prevention of aortic root dilatation are advised to continue throughout pregnancy, particularly in the third trimester and peripartum period. Strict blood pressure control is mandatory in all aortopathies during pregnancy. Women with MFS with dilated aortic root 4.0 to 4.5 cm, BAV above 5.0 cm, and Turner syndrome with an indexed aorta >25 mm/m^2 should receive careful counseling from cardiology, cardiac surgery, and maternal fetal medicine, and strongly consider root replacement before pregnancy (1).

RESUSCITATION MEDICATIONS DURING PREGNANCY

Maternal life-saving medications should not be withheld during emergency situations such as cardiogenic shock or cardiac arrest. Post-arrest considerations are similar to those of nonpregnant patients. β-blockers are used as first line for arrhythmia suppression and long QT syndrome (38).

CONCLUSIONS

CVD is the leading cause of nonobstetric maternal death in pregnancy. The use of CVD medications during pregnancy requires knowledge of the physiological changes of pregnancy, which may alter the drug's properties, as well as the fetal effects of these medications. A multidisciplinary team should provide thoughtful and complete counseling to the pregnant woman with CVD disease regarding the risks and benefits of medication use. As our understanding of pregnancy physiology, pharmacology, and the fetal and placental interactions continues to evolve, we will have an improved ability to treat maternal CVD conditions during pregnancy.

ACKNOWLEDGMENTS The authors acknowledge Dr. Frank Cecchin for his valuable input and Abigail Moses for her assistance in the creation of the **Central Illustration**.

ADDRESS FOR CORRESPONDENCE: Dr. Dan G. Halpern, Adult Congenital Heart Disease Program, New York University School of Medicine, The Leon H. Charney Division of Cardiology, NYU Langone Health, 530 First Avenue, HCC building 7H, New York, New York 10016. E-mail: dan.halpern@nyumc.org. Twitter: @nyulangone.

REFERENCES

1. Regit-Azgrosek V, Roos-Hesselink JW, Bauersachs J, et al., ESC Scientific Document Group. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39:3165–241.

2. Creanga AA, Syverson C, Seed K, et al. Pregnancy-related mortality in the United States, 2011-2013. Obstet Gynecol 2017;130:366–73.

3. Peters RM, Flack JM. Hypertensive disorders of pregnancy. J Obstet Gynecol Neonatal Nurs 2004;33:209–20.

4. Kuklina E, Callaghan W. Chronic heart disease and severe obstetric morbidity among hospitalisations for pregnancy in the USA: 1995-2006. BJOG 2011;118:345–52.

5. Ruys TP, Maggioni A, Johnson MR, et al. Cardiac medication during pregnancy, data from the ROPAC. Int J Cardiol 2014;177:124–8.

6. Nanna M, Stergiopoulos K. Pregnancy complicated by valvular heart disease: an update. J Am Heart Assoc 2014;3:e000712.

7. Easterling TR, Benedetti TJ, Schmucker BC, Carlson K, Millard SP. Maternal hemodynamics and aortic diameter in normal and hypertensive pregnancies. Obstet Gynecol 1991;78:1073–7.

8. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation 2014;130:1003–8.

9. Robson SC, Hunter S, Moore M, Dunlop W. Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. Br J Obstet Gynaecol 1987;94:1028–39.

10. Pariente G, Leibson T, Carls A, Adams-Webber T, Ito S, Koren G. Pregnancy-associated changes in pharmacokinetics: a systematic review. PLoS Med 2016;13:e1002160.

11. Parry E, Shields R, Turnbull AC. Transit time in the small intestine in pregnancy. J Obstet Gynaecol Br Commonw 1970;77:900–1.

12. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. Clinical Pharmacokinetics 1997;33:328–43.

13. Carter BL, Garnett WR, Pellock JM, Stratton MA, Howell JR. Effect of antacids on phenytoin bioavailability. Ther Drug Monit 1981;3:333–40.

14. O'Hare MF, Leahey W, Murnaghan GA, McDevitt DG. Pharmacokinetics of sotalol during pregnancy. Eur J Clin Pharmacol 1983;24:521–4.

15. O'Hare MF, Kinney CD, Murnaghan GA, McDevitt DG. Pharmacokinetics of propranolol during pregnancy. Eur J Clin Pharmacol 1984;27:583–7.

16. Anderson GD. Using pharmacokinetics to predict the effects of pregnancy and maternal-infant transfer of drugs during lactation. Expert Opin Drug Metab Toxicol 2006;2:947–60.

17. Anger GJ, Piquette-Miller M. Pharmacokinetic studies in pregnant women. Clin Pharmacol Ther 2008;83:184–7.

18. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. Semin Perinatol 2015;39:512–9.

19. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol 2014;5:65.

20. Tracy TS, Venkataramanan R, Glover DD, Caritis SN, for the National Institute for Child Health and Human Development Network of Maternal-Fetal-Medicine Units. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obs Gyn 2005;192:633–9.

21. Wadelius M, Darj E, Frenne G, Rane A. Induction of CYP2D6 in pregnancy. Clin Pharmacol Ther 1997;62:400–7.

22. Rogers RC, Sibai BM, Whybrew WD. Labetalol pharmacokinetics in pregnancy-induced hypertension. Am J Obstet Gynecol 1990;162:362–6.

23. Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy. Kidney Int 1980;18:152–61.

24. Davison JM, Noble MC. Serial changes in 24 hour creatinine clearance during normal menstrual cycles and the first trimester of pregnancy. Br J Obstet Gynaecol 1981;88:10–7.

25. Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis 2013;20:209–14.

26. Little B. Water and electrolyte balance during pregnancy. Anesthesiology 1965;26:400–8.

27. Moran P, Lindheimer MD, Davison JM. The renal response to preeclampsia. Semin Nephrol 2004;24:588–95.

28. Hebert MF, Carr DB, Anderson GD, et al. Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum. J Clin Pharmacol 2005;45:25–33.

29. Hurst AK, Shotan A, Hoffman K, et al. Pharmacokinetic and pharmacodynamic evaluation of atenolol during and after pregnancy. Pharmacotherapy 1998;18:840–6.

30. Collins TF. History and evolution of reproductive and developmental toxicology guidelines. Curr Pharm Des 2006;12:1449–65.

31. Plank LS. Governmental oversight of prescribing medications: history of the US Food and Drug Administration and prescriptive authority. J Midwifery Womens Health 2011;56:198–204.

32. U.S. Food and Drug Administration. Milestones in U.S. Food and Drug Law History. 2018. Available at: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm2007256.htm. Accessed March 6, 2018.

33. Federal Register. Part 201 (21 CFR part 201) (44 FR 37434, June 26, 1979). Available at: https://www.govinfo.gov/content/pkg/FR-2014-12-04/pdf/2014-28241.pdf. Accessed December 29, 2018.

34. Brucker MC, King TL. The 2015 US Food and Drug Administration Pregnancy and Lactation Labeling Rule. J Midwifery Womens Health 2017;62:308–16.

35. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects–Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep 2008;57:1–5.

36. American College of Obstetricians and Gynecologists. Frequently Asked Questions: Miscarriage and Molar Pregnancy, August 2015. Available at: https://www.acog.org/-/media/For-Patients/faq090.pdf. Accessed March 6, 2018.

37. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338:1128–37.

38. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. Circulation 2015;132:1747–73.

39. Enriquez AD, Economy KE, Tedrow UB. Contemporary management of arrhythmias during pregnancy. Circ Arrhythm Electrophysiol 2014;7:961–7.

40. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. Clin Cardiol 2008;31:538–41.

41. Thaman R, Curtis S, Faganello G, et al. Cardiac outcome of pregnancy in women with a pacemaker and women with untreated atrioventricular conduction block. Europace 2011;13:859–63.

42. Natale A, Davidson T, Geiger MJ, Newby K. Implantable cardioverter-defibrillators and pregnancy: a safe combination? Circulation 1997;96:2808–12.

43. Lee SH, Chen SA, Wu TJ, et al. Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. Am J Cardiol 1995;76:675–8.

44. Elkayam U, Goodwin TM. Adenosine therapy for supraventricular tachycardia during pregnancy. Am J Cardiol 1995;75:521–3.

45. Matsubara S, Kuwata T, Mitsuhashi T. Adenosine for maternal supraventricular tachycardia and preterm delivery. J Obstet Gynaecol Can 2011;33:794–5.

46. Duan L, Ng A, Chen W, et al. Beta-blocker exposure in pregnancy and risk of fetal cardiac anomalies. JAMA Intern Med 2017;177:885–7.

47. Bergman JEH, Lutke LR, Gans ROB, et al. Beta-blocker use in pregnancy and risk of specific congenital anomalies: a European case-malformed control study. Drug Saf 2018;41:415–27.

48. Yakoob MY, Bateman BT, Ho E, et al. The risk of congenital malformations associated with exposure to beta-blockers early in pregnancy: a meta-analysis. Hypertension 2013;62:375–81.

49. Van Zutphen AR, Werler MM, Browne MM, et al. Maternal hypertension, medication use, and hypospadias in the National Birth Defects Prevention Study. Obstet Gynecol 2014;123 Pt 1:309–17.

50. Bateman BT, Patorno E, Desai RJ, et al. Late pregnancy beta blocker exposure and risks of neonatal hypoglycemia and bradycardia. Pediatrics 2016;138:e20160731.

51. Meidahl Petersen K, Jimenez-Solem E, Andersen JT, et al. beta-Blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study. BMJ Open 2012;2:e001185.

52. Ersbøll AS, Hedegaard M, Søndergaard L, Ersbøll M, Johansen M. Treatment with oral beta-blockers during pregnancy complicated by maternal heart disease increases the risk of fetal growth restriction. BJOG 2014;121:618–26.

53. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens 1999;12:541–7.

54. Lip GY, Beevers M, Churchill D, Shaffer LM, Beevers DG. Effect of atenolol on birth weight. Am J Cardiol 1997;79:1436–8.

55. Satgé D, Sasco AJ, Col JY, Lemonnier PG, Hemet J, Robert E. Antenatal exposure to atenolol and retroperitoneal fibromatosis. Reprod Toxicol 1997;11:539–41.

56. Pruyn SC, Phelan JP, Buchanan GC. Long-term propranolol therapy in pregnancy: maternal and fetal outcome. Am J Obstet Gynecol 1979;135:485–9.

57. Ryu RJ, Eyal S, Easterling TR, et al. Pharmacokinetics of metoprolol during pregnancy and lactation. J Clin Pharmacol 2016;56:581–9.

58. Högstedt S, Rane A. Plasma concentration—effect relationship of metoprolol during and after pregnancy. Eur J Clin Pharmacol 1993;44:243–6.

59. Davis RL, Eastman D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to calcium channel and beta-blockers during pregnancy. Pharmacoepidemiol Drug Saf 2011;20:138–45.

60. Bateman BT, Huybrechts KF, Maeda A, et al. Calcium channel blocker exposure in late pregnancy and the risk of neonatal seizures. Obstet Gynecol 2015;126:271–8.

61. Weber-Schoendorfer C, Hannemann D, Meister R, et al. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. Reprod Toxicol 2008;26:24–30.

62. Cleary-Goldman J, Salva CR, Infeld JI, et al. Verapamil-sensitive idiopathic left ventricular tachycardia in pregnancy. J Matern Fetal Neonatal Med 2003;14:132–5.

63. Byerly WG, Hartmann A, Foster DE, Tannenbaum AK. Verapamil in the treatment of maternal paroxysmal supraventricular tachycardia. Ann Emerg Med 1991;20:552–4.

64. Klein V, Repke JT. Supraventricular tachycardia in pregnancy: cardioversion with verapamil. Obstet Gynecol 1984;63 Suppl:16S–8S.

65. Mitani GM, Steinberg I, Lien EJ, Harrison EC, Elkayam U. The pharmacokinetics of antiarrhythmic agents in pregnancy and lactation. Clin Pharmacokinet 1987;12:253–91.

66. Kates RE. Calcium antagonists. Drugs 1983;25:113–24.

67. Shen O, Entebi E, Yagel S. Congenital hypertrophic cardiomyopathy associated with in utero verapamil exposure. Prenat Diagn 1995;15:1088–9.

68. El-Sayed YY, Holbrook RH Jr., Gibson R, Chitkara U, Druzin ML, Baba D. Diltiazem for maintenance tocolysis of preterm labor: comparison to nifedipine in a randomized trial. J Matern Fetal Med 1998;7:217–21.

69. Khandelwal M, Kumanova M, Gaughan JP, Reece EA. Role of diltiazem in pregnant women with chronic renal disease. J Matern Fetal Neonatal Med 2002;12:408–12.

70. Chaffman M, Brogden RN. Diltiazem. Drugs 1985;29:387–454.

71. Okada M, Inoue H, Nakamura Y, Kishimoto M, Suzuki T. Excretion of diltiazem in human milk. N Engl J Med 1985;312:992–3.

72. Soyka LF. Digoxin: placental transfer, effects on the fetus, and therapeutic use in the newborn. Clin Perinatol 1975;2:23–35.

73. Gonser M, Stoll P, Kahle P. Clearance prediction and drug dosage in pregnancy. Clin Drug Invest 1995;9:197–205.

74. Hebert MF, Easterling TR, Kirby B, et al. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a University of Washington

specialized center of research study. Clin Pharmacol 2008;84:248–53.

75. Graves SW, Valdes R Jr., Brown BA, Knight AB, Craig HR. Endogenous digoxin-immunoreactive substance in human pregnancies. J Clin Endocrinol Metab 1984;58:748–51.

76. Saad AF, Monsivais L, Pacheco LD. Digoxin therapy of fetal superior ventricular tachycardia: are digoxin serum levels reliable? AJP Rep 2016;6:e272–6.

77. Rogers MC, Willerson JT, Goldblatt A, Smith TW. Serum digoxin concentrations in the human fetus, neonate and infant. N Engl J Med 1972;287:1010–3.

78. Villanova C, Muriago M, Nava F. Arrhythmogenic right ventricular dysplasia: pregnancy under flecainide treatment. G Ital Cardiol 1998;28:691–3.

79. Connaughton M, Jenkins BS. Successful use of flecainide to treat new onset maternal ventricular tachycardia in pregnancy. Br Heart J 1994;72:297.

80. Krapp M, Baschat AA, Gembruch U, Geipel A, Germer U. Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. Ultrasound Obstet Gynecol 2002;19:158–64.

81. Ebenroth ES, Cordes TM, Darragh RK. Second-line treatment of fetal supraventricular tachycardia using flecainide acetate. Pediatr Cardiol 2001;22:483–7.

82. Wren C, Hunter S. Maternal administration of flecainide to terminate and suppress fetal tachycardia. Br Med J (Clin Res Ed) 1988;296:249.

83. Kofinas AD, Simon NV, Sagel H, Lyttle E, Smith N, King K. Treatment of fetal supraventricular tachycardia with flecainide acetate after digoxin failure. Am J Obstet Gynecol 1991;165:630–1.

84. Sridharan S, Sullivan I, Tomek V, et al. Flecainide versus digoxin for fetal supraventricular tachycardia: comparison of two drug treatment protocols. Heart Rhythm 2016;13:1913–9.

85. Strizek B, Berg C, Gottschalk I, Herberg U, Geipel A, Gembruch U. High-dose flecainide is the most effective treatment of fetal supraventricular tachycardia. Heart Rhythm 2016;13:1283–8.

86. Capucci A, Boriani G. Propafenone in the treatment of cardiac arrhythmias. A risk-benefit appraisal. Drug Saf 1995;12:55–72.

87. Libardoni M, Piovan D, Busato E, Padrini R. Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk. Br J Clin Pharmacol 1991;32:527–8.

88. Santinelli V, Turco P, De Paola M, et al. Propafenone in Wolff-Parkinson-White syndrome at risk. Cardiovasc Drug Ther 1990;4:681–5.

89. Brunozzi LT, Meniconi L, Chiocchi P, Liberati R, Zuanetti G, Latini R. Propafenone in the treatment of chronic ventricular arrhythmias in a pregnant patient. Br J Clin Pharmacol 1988;26:489–90.

90. Juneja MM, Ackerman WE, Kaczorowski DM, Sollo DG, Gunzenhauser LF. Continuous epidural lidocaine infusion in the parturient with paroxysmal ventricular tachycardia. Anesthesiology 1989;71:305–8.

91. Menon KP, Mahapatra RK. Paroxysmal ventricular tachycardia associated with Bell's palsy in a teenager at late pregnancy. Angiology 1984;35:534–6.

92. Gregg AR, Tomich PG. Mexilitene use in pregnancy. J Perinatol 1988;8:33–5.

93. Sharif-Kazemi MB, Emkanjoo Z, Tavoosi A, et al. Electrical storm in Brugada syndrome during pregnancy. Pacing Clin Electrophysiol 2011;34:e18–21.

94. Allen NM, Page RL. Procainamide administration during pregnancy. Clin Pharm 1993;12:58–60.

95. Latini R, Tognoni G, Kates RE. Clinical pharmacokinetics of amiodarone. Clin Pharmacokinet 1984;9:136–56.

96. Lomenick JP, Jackson WA, Backeljauw PF. Amiodarone-induced neonatal hypothyroidism: a unique form of transient early-onset hypothyroidism. J Perinatol 2004;24:397–9.

97. Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. J Endocrinol Invest 2001;24:116–30.

98. Pézard PG, Boussion F, Sentilhes L, et al. Fetal tachycardia: a role for amiodarone as first- or second-line therapy? Arch Cardiovasc Dis 2008;101:619–27.

99. Capone CA, Gebb J, Dar P, Shenoy RU. Favorable neurodevelopmental outcome in a hypothyroid neonate following intracordal amiodarone for cardioversion of refractory supraventricular tachycardia in a fetus. J Neonatal Perinatal Med 2014;7:305–9.

100. Grosso S, Berardi R, Cioni M, Morgese G. Transient neonatal hypothyroidism after gestational exposure to amiodarone: a follow-up of two cases. J Endocrinol Invest 1998;21:699–702.

101. Mikovic Z, Karadzov N, Jovanovic I, et al. Developmental delay associated with normal thyroidal function and long-term amiodarone therapy during fetal and neonatal life. Biomed Pharmacother 2010;64:396–8.

102. Valensise H, Civitella C, Garzetti GG, Romanini C, et al. Amiodarone treatment in pregnancy for dilatative cardiomyopathy with ventricular malignant extrasystole and normal maternal and neonatal outcome. Prenat Diagn 1992;12:705–8.

103. Strunge P, Frandsen J, Andreasen F. Amiodarone during pregnancy. Eur Heart J 1988;9:106–9.

104. Oudijk MA, Michon MM, Kleinman CS, et al. Sotalol in the treatment of fetal dysrhythmias. Circulation 2000;101:2721–6.

105. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. Nat Clin Pract Nephrol 2007;3:613–22.

106. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.

107. Pauli JM, Repke JT. Pitfalls with the New American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Clin Obstet Gynecol 2017;60:141–52.

108. Seely EW, Ecker J. Chronic hypertension in pregnancy. Circulation 2014;129:1254–61.

109. Magee LA, Singer J, von Dadelszen P, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 2015;372:2367–8.

110. Amro FH, Moussa HN, Ashimi OA, Sibai BM. Treatment options for hypertension in pregnancy and puerperium. Expert Opin Drug Saf 2016;15:1635–42.

111. 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;2:419–36.

112. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2014;2:CD002252.

113. Fischer JH, Sarto GE, Hardman J, et al. Influence of gestational age and body weight on the pharmacokinetics of labetalol in pregnancy. Clin Pharmacokinet 2014;53:373–83.

114. Clark SM, Dunn HE, Hankins GD. A review of oral labetalol and nifedipine in mild to moderate hypertension in pregnancy. Semin Perinatol 2015;39:548–55.

115. van Vliet EO, Schuit E, Heida KY. Nifedipine versus atosiban in the treatment of threatened preterm labour (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour: APOSTEL III-Trial). BMC Pregnancy Childbirth 2014;14:93.

116. Bateman BT, Hernandez-Diaz S, Huybrechts KF, et al. Outpatient calcium-channel blockers and the risk of postpartum haemorrhage: a cohort study. BJOG 2013;120:1668–76.

117. Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet 1982;1:647–9.

118. Slim R, Ben Salem C, Hmouda H, Bouraoui K. Hepatotoxicity of alpha-methyldopa in pregnancy. J Clin Pharm Ther 2010;5:361–3.

119. Canobbio MM, Warnes CA, Aboulhosn J, et al. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2017;135:e50–87.

120. Gudmundsson S, Gennser G, Marsal K. Effects of hydralazine on placental and renal circulation in pre-eclampsia. Acta Obstet Gynecol Scand 1995;74:415–8.

121. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ 2003;327:955–60.

122. Horvath JS, Phippard A, Korda A, Henderson-Smart DJ, Child A, Tiller DJ. Clonidine hydrochloride–a safe and effective antihypertensive agent in pregnancy. Obstet Gynecol 1985;66:634–8.

123. Buchanan ML, Easterling TR, Carr DB. Clonidine pharmacokinetics in pregnancy. Drug Metab Dispos 2009;37:702–5.

124. Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. Br Med J (Clin Res Ed) 1985;290:17–23.

125. Olesen C, de Vries CS, Thrane N. Effect of diuretics on fetal growth: a drug effect or confounding

by indication? Pooled Danish and Scottish cohort data. Br J Clin Pharmacol 2001;51:153–7.

126. Bowen ME, Ray WA, Arbogast PG, Ding H, Cooper WO. Increasing exposure to angiotensin-converting enzyme inhibitors in pregnancy. Am J Obstet Gynecol 2008;198:291. e1–5.

127. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.

128. Tanaka K, Tanaka H, Kamiya C, et al. Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. Circ J 2016;80:2221–6.

129. Bauersachs J, Arrigo M, Hilfiker-Kleiner D. Current management of patients with severe acute peripartum cardiomyopathy: practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. Eur J Heart Fail 2016;18:1096–105.

130. Van Nimwegen D, Dyer DC. The action of vasopressors on isolated uterine arteries. Am J Obstet Gynecol 1974;118:1099–103.

131. Hilfiker-Kleiner D, Haghikia A, Berliner D. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. Eur Heart J 2017;38:2671–9.

132. Abdalla M, Mancini DM. Management of pregnancy in the post-cardiac transplant patient. Semin Perinatol 2014;38:318–25.

133. Elkayam U, Jalnapurkar S, Barakkat MN, et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. Circulation 2014;129:1695–702.

134. Lameijer H, Kampman MA, Oudijk MA, Pieper PG. Ischaemic heart disease during pregnancy or post-partum: systematic review and case series. Neth Heart J 2015;23:249–57.

135. Ladner HE, Danielsen B, Gilbert WM. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. Obstet Gynecol 2005;105:480–4.

136. Winterfeld U, Allignol A, Panchaud A. Pregnancy outcome following maternal exposure to statins: a multicentre prospective study. BJOG 2013;120:463–71.

137. Karalis DG, Hill AN, Clifton S, Wild RA. The risks of statin use in pregnancy: A systematic review. J Clin Lipidol 2016;10:1081–90.

138. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. N Engl J Med 2004;350:1579–82.

139. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. BMJ 2015;350:h1035.

140. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. J Clin Lipidol 2015;9 Suppl. S1–122.e1.

141. Armstrong EM, Bellone JM, Hornsby LB, et al. Pregnancy-related venous thromboembolism. J Pharm Pract 2014 Jun;27:243–52.

142. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis 2016;41:92–128.

143. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

144. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol 1999;33:1637–41.

145. Dilli D, Oğuz S, Dilmen U. A case of congenital warfarin syndrome due to maternal drug administration during the pregnancy. Genet Couns 2011;22:221–6.

146. Stevenson RE, Burton OM, Ferlauto GJ, Taylor HA. Hazards of oral anticoagulants during pregnancy. JAMA 1980;243:1549–51.

147. Kumar M, Bhasker SK, Singh R, Kohli N, Kumar R. Di Sala syndrome. BMJ Case Rep 2012;2012. bcr1220115291.

148. Elkayam U, Goland S. The search for a safe and effective anticoagulation regimen in pregnant women with mechanical prosthetic heart valves. J Am Coll Cardiol 2012;59:1116–8.

149. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation 2015;132:132–42.

150. Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. J Am Coll Cardiol 2017;69:2681–91.

151. Knol HM, Schultinge L, Erwich JJ, Meijer K. Fondaparinux as an alternative anticoagulant therapy during pregnancy. J Thromb Haemost 2010;8:1876–9.

152. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 2007;369:1791–8.

153. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994;343:619–29.

154. Yarrington CD, Valente AM, Economy KE. Cardiovascular management in pregnancy: antithrombotic agents and antiplatelet agents. Circulation 2015;132:1354–64.

155. De Santis M, De Luca C, Mappa I, et al. Clopidogrel treatment during pregnancy: a case report and a review of literature. Intern Med 2011;50:1769–73.

156. Tello-Montoliu A, Seecheran NA, Angiolillo DJ. Successful pregnancy and delivery on prasugrel treatment: considerations for the use of dual antiplatelet therapy during pregnancy in clinical practice. J Thromb Thrombolysis 2013;36:348–51.

157. Pieper PG, Lameijer H, Hoendermis ES. Pregnancy and pulmonary hypertension. Best Pract Res Clin Obstet Gynaecol 2014;28:579–91.

158. Bassily-Marcus AM, Yuan C, Oropello J, Manasia A, Kohli-Seth R, Benjamin E. Pulmonary hypertension in pregnancy: critical care management. Pulm Med 2012;2012:709407.

159. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the Registry Of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. Eur J Heart Fail 2016;18:1119–28.

160. Hemnes AR, Kiely DG, Cockrill BA, et al. Statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute. Pulm Circ 2015;5:435–65.

161. Tabarsi N, Levy R, Rychel V, et al. Pregnancy among women with pulmonary arterial hypertension: a changing landscape? Int J Cardiol 2014;177:490–1.

162. Elliot CA, Stewart P, Webster VJ, et al. The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. Eur Respir J 2005;26:168–73.

163. Horng M, Mohammad I, Smith ZR, Awdish RL, Cajigas HR. Inhaled iloprost for chronic thromboembolic pulmonary hypertension (CTEPH) during pregnancy: a case report. Pharmacotherapy 2016;36:e142–7.

164. Curry RA, Fletcher C, Gelson E, et al. Pulmonary hypertension and pregnancy-a review of 12 pregnancies in nine women. BJOG 2012;119:752–61.

165. Goland S, Tsai F, Habib M, Janmohamed M, Goodwin TM, Elkayam U. Favorable outcome of pregnancy with an elective use of epoprostenol and sildenafil in women with severe pulmonary hypertension. Cardiology 2010;115:205–8.

166. Elkayam U, Ostrzega E, Shotan A, Mehra A. Cardiovascular problems in pregnant women with the Marfan syndrome. Ann Intern Med 1995;123:117–22.

167. Karnis MF, Zimon AE, Lalwani SI, et al. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. Fertil Steril 2003;80:498–501.

168. Immer FF, Bansi AG, Immer-Bansi AS, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. Ann Thorac Surg 2003;76:309–14.

KEY WORDS cardiovascular medications, gestation, pharmacokinetics, pregnancy