

APPENDIX 5

AHA 2017 Statement on Pregnancy in ACHD. Medications During Pregnancy

	Common Examples	FDA Pregnancy Category	Teratogenic Risks (First Trimester)	Other Pregnancy Concerns (Second and Third Trimesters)	Suggested Evaluation	Lactation	Notes
Antihypertensives							
β -Blockers	Metoprolol Propranolol Carvedilol Atenolol	C C C D	None reported	Possible association with fetal growth restriction in second and third trimesters (atenolol, propranolol), neonatal bradycardia (esmolol, nadolol)	Consider serial fetal sonography to assess interval fetal growth in second and third trimesters	Except for atenolol, probably safe	
Combined α -/ β -blockers	Labetalol	C	None reported	No		Yes	
Calcium channel blockers	Nifedipine Verapamil Diltiazem	C	None reported	Caution if used in combination with magnesium sulfate		Yes	
ACE inhibitors	Captopril Enalapril Lisinopril	C (first trimester) D (second and third trimesters)		Fetal renal dysplasia, oligohydramnios, growth restriction, and intrauterine demise reported in second and third trimesters	Consider fetal echocardiography with first trimester exposure, serial sonography to assess interval fetal growth and amniotic fluid volume in second and third trimesters	Yes (captopril and enalapril) Unknown (lisinopril)	Avoid if possible during pregnancy
α_2 -Adrenergic agonists	Methyldopa Clonidine	B C	None reported	Induction of positive indirect Coombs testing (methyldopa), rare neonatal hypertension (clonidine)		Yes (methyldopa) Probably safe (clonidine)	
Vasodilators	Hydralazine Epoprostenol Nitroprusside Nitroglycerin Isosorbide dinitrate Sildenafil	C B B	None reported	Possible transient fetal bradycardia (nitroprusside)		Yes (hydralazine) Probably safe (nitroglycerin) Unknown (epoprostenol, nitroprusside, isosorbide dinitrate, sildenafil)	
Diuretics							
Thiazide diuretics	Hydrochlorothiazide	B	None reported	Possible increased risk of neonatal hypoglycemia and thrombocytopenia	Consider neonatal blood count and electrolyte evaluation	Yes (AAP) No (WHO)	Maintenance therapy permissible, but therapy not usually started during

Loop of Henle diuretics	Furosemide	C	None reported	Possible association with neonatal PDA and sensorineural hearing loss	Maternal electrolyte monitoring	No	
Potassium-sparing diuretics	Spironolactone (not recommended)	C	None reported			Yes (probably safe; (not recommended)	
Anticoagulants							
Heparin (including LMWHs)	Heparin Enoxaparin Dalteparin	C	None reported	Possible maternal osteoporosis, heparin-induced thrombocytopenia, and bleeding	Maternal platelet and coagulation status monitoring (as appropriate)	Yes	
Vitamin K antagonists	Warfarin	X	Fetal warfarin syndrome (craniofacial and skeletal anomalies) with exposure in weeks 6–9; fetal intracranial hemorrhage in second and third trimesters		Comprehensive fetal sonography at 18–20 wk of gestation	Yes 	Teratogenicity appears to be related to doses >5 mg daily
Antiplatelet agents	Aspirin (full dose)	D (third trimester)	None reported	Premature closure of fetal ductus arteriosus at ≥32 wk of gestation		Unknown (AAP) No (WHO)	Low-dose aspirin (≤100 mg/d) does not appear to have deleterious effects
	Clopidogrel	B			Empirical recommendation to discontinue clopidogrel 7 d in advance of anticipated delivery		
Direct thrombin inhibitors	Argatroban	B	None reported			Unknown	
Indirect factor Xa inhibitors	Fondaparinux	B	None reported	Possible neonatal factor Xa inhibition		Unknown	
Direct factor Xa inhibitors	Rivaroxaban	C	None reported	Theoretical risk of maternal hemorrhage		Unknown	
Fibrinolytics	Streptokinase	C	None reported			Unknown	
Inotropic/vasopressors							
Cardiac glycosides	Digoxin Digitoxin	C	None reported			Yes	

Adrenergic agents	Epinephrine Norepinephrine Phenylephrine Dopamine Isoproterenol	C	Possible association with gastroschisis or hemifacial microsomia (phenylephrine)			Probably safe (dopamine) Unknown (epinephrine, norepinephrine, phenylephrine, isoproterenol)	
Antiarrhythmics							
β-Blockers	Metoprolol Propranolol Carvedilol Atenolol	C C C D	None reported	Association with fetal growth restriction in second and third trimesters (atenolol, propranolol), neonatal bradycardia (esmolol, nadolol)	Consider serial fetal sonography to assess interval fetal growth in second and third trimesters	Except for atenolol, probably safe	
Class 1A	Quinidine Procainamide	C C	None reported			Yes	
Class 1C	Flecainide	C	None reported			Yes	
Class III	Sotalol Amiodarone	B D	None reported	Thyroid dysfunction		No No WHO/ (AAP Yes)	
Purine nucleosides	Adenosine	C	None reported			Unknown	

FDA Drug Classifications

Rating A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester; no evidence of a risk.
Rating B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
Rating C	Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Rating D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Rating X	Studies in animals or human beings have demonstrated fetal abnormalities, there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

AAP indicates American Academy of Pediatrics; ACE, angiotensin-converting enzyme; FDA, US Food and Drug Administration; LMWH, low molecular weight heparin; PDA, patent ductus arteriosus; and WHO, World Health Organization.

Note: The FDA A to X categories of drugs—the classification system for counselling of pregnant women requiring drug therapy—was replaced by the Pregnancy and Lactation Labelling Rule, which provides a descriptive risk summary and detailed information on animal and clinical data, by the US FDA in June 2015

Management of Pregnancy in Patients With Complex Congenital Heart Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation* 2017

2023 HRS expert consensus statement on the management of arrhythmias during pregnancy.

Antiarrhythmic drugs for use in pregnancy

Drug	Therapeutic maternal dose range ¹	Therapeutic maternal serum level	Toxicity/adverse events	
			Maternal	Fetal/neonatal
Digoxin ^{80,82,97-100} (mat/fetal PO, IV, direct fetal IM, IC)	LD: 1.5-2.0 mg/24 h PO/IV, divided Q 8 h MD: 0.125-0.5 mg/day PO, divided BID DFR: (fetal IM dose 88 µg/kg, then 60-88 µg/kg fetal IM Q 12 h × 2)	0.7-2.0 ng/mL F/M ratio @ 50-100%; in hydrops 20%	N/V+++, anorexia++, sinus bradycardia+ or Mobitz I AV block+, proarrhythmia +, avoid in WPW	Fetal IM: sciatic nerve injury (~1:40 risk); fetal IC: cardiac arrest, consider IC or ICad epinephrine if this occurs Infant: Usually well tolerated, often used in combination, vomiting ++, sinus bradycardia++, AV block, proarrhythmia
Class IA: Na⁺ channel blockers				
Procainamide ^{83,96} (mat IV, +/- PO)	LD: 15 mg/kg IV over 30 min MD: 1-4 mg/min infusion	4-8 µg/mL	N/V+, TdP, ↑QTc, IV, uterine irritability, preterm labor	Neonatal TdP+, ↑QTc
Quinidine gluconate ¹⁰¹⁻¹⁰³ (mat/fetal IV, PO)	LD: 200-400 mg PO Q 2-3 h until therapeutic effect (max 3 g/day) MD: XR 324-648 mg Q 8-12 h Parenteral: 10 mg/kg over 1-2 h, then 0.02 mg/kg/min × 72 h	2-6 mg/L F/M ratio 30-100%	N/V+++, CNS+, ↑QTc+, proarrhythmia, TdP	Neonatal TdP, concentrates in breast milk
Class IB: Na⁺ channel blockers				
Lidocaine ¹⁰⁴⁻¹⁰⁶ (mat/fetal IV)	LD: 1-1.5 mg/kg LD IV, 300 mg max MD: infusion of 1-4 mg/min	1.5-5 µg/mL F/M ratio 1:1	N/V+, CNS+, proarrhythmia (consider all sources of lidocaine, including regional anesthesia) can halt labor	CNS++, bradycardia during labor (consider all sources of lidocaine, including regional anesthesia)
Mexiletine ¹⁰⁷ (mat/fetal PO)	LD: 6-8 mg mg/kg/day Q 8-12 h (up to 400 mg Q 8 h or 450 mg Q 12 h) MD: 200-300 mg TID	0.5-2 µg/mL F/M ratio 1:1	NV++, CNS++, proarrhythmia	CNS++, concentrates in breast milk
Class IC: Na⁺ channel blockers				
Flecainide ^{90,98,108-111} (mat/fetal PO)	MD: 200-400 mg/day divided Q 8-12 h PO Avoid in SHD	0.2-1.0 µg/mL F/M ratio 50-86%	Visual/CNS++, mild P/QRS widening + and 1° AV block+, ↑QTc, AFL	Fetal/neonatal QRS widening with longer exposure (drug concentrates in amniotic fluid); ↑QTc+, proarrhythmia+; well tolerated in infants, commonly combined with other drugs
Propafenone ¹¹²⁻¹¹⁵ (mat/fetal PO)	MD: 150 mg Q 8 h, increase slowly (max 900 mg/day), extended release 225-425 Q 12 h PO Avoid in SHD	500-600 ng/mL (range 65-1000) F/M ratio NA	CNS++, ↑QTc, GI+, QRS widening, AFL, bradycardia	CNS+, little data

Class II: Beta-blockers

Propranolol ^{88,116-121} (mat/fetal PO, IV)	MD: 60-320 mg/day divided Q 6-12 h Parenteral (caution): 1-3 mg IV at <1 mg/min, can repeat once; reserve for life-threatening arrhythmia	25-140 ng/mL F/M ratio 0.4	Fatigue ++, bradycardia ++, hypotension ++, AV block, ↑ uterine tone
Metoprolol ^{116,122,123} (mat/fetal PO/IV)	MD: 50-450 mg/day PO, divided BID if SR or Q 6 h if standard Parenteral (caution): 5 mg Q 2 min × 3 then change to PO; for HTN, labetalol preferred	5-10 ng/mL	Similar to propranolol
Nadolol ^{116,122} (mat PO)	MD: 40-80 mg/day PO; up to 240 mg has been used	Not used clinically	Same as other beta-blockers; noncompliant patients may maintain levels due to long T _{1/2}

Class III: K⁺ channel blockers and multimechanism

Sotalol ^{75,78,80,81,87,98-100,108,115,124,125} (mat/fetal PO, mat PO/IV)	MD: 160-320 mg/day divided BID or Q 8 h Parenteral for life-threatening maternal arrhythmia: 75-150 mg IV Q day or BID (if QTc <450 ms)	200-1000 ng/mL, fetal can be > maternal, F/M ratio 100-107%	N/V/fatigue/CNS ++, sinus bradycardia +, ↑ QTc (hold or reduce dose if QTc >500 ms), proarrhythmia	CNS, +/- proarrhythmia, bradycardia +, (concentrates in amniotic fluid), rare ↑ QTc; well tolerated in infants
Amiodarone ^{106,108,126-130} (mat/fetal PO, mat IV, DFT)	LD: 1800-2400 mg/day PO divided Q 6 h × 48 h; lower LD (1200 mg) if concurrent drug therapy; no fetal advantage to maternal IV dosing Maternal parenteral LD: 1000 mg over 24 h as 150 mg/10 min, then 360 mg/6 h, then 540 mg/18 h IV MD: 800 mg × 1 wk, then 200-600 mg/day Maternal parenteral MD: 0.5 mg/min IV up to 3 wk Cardiac arrest: 5 mg/kg (max 300 mg) rapid IV/IO/ET, repeat 1-2× DFT (hydrops only): IC 2.5-5 mg/kg nonhydropic fetal weight up to 40 mg, diluted with glucose and given over 5-10 min; intraperitoneal 50-75 mg in D5W, repeat as needed, can remove excess ascitic fluid prior to amiodarone administration	0.7-2.8 µg/mL F/M ratio 10-30%, but efficacy over time is seen due to fatty-tissue accumulation	NV ++, ↑ thyroid ++, sinus bradycardia ++, ↓ appetite, 1° AV block, P/QRS widening, ↑ QTc, proarrhythmia, photosensitivity rash, TdP, ↑ other drug concentrations (digoxin, flecainide), liver and lung toxicity with chronic use Parenteral: hypotension if doses >2100 mg/24 h	↑ Thyroid ++, fetal TdP if given for LQTS, goiter, neurodevelopmental concerns Intracondal: fetal death ++ Intraperitoneal: possible GI adhesions (1 report only) Amiodarone, despite its side effects, can allow fetal survival in severe cases, especially prior to preterm delivery of a severely hydropic fetus <35 wk GA; often used in combination with other drugs, and may take several weeks to slow, and then terminate tachycardia Absence of progression of hydrops is usually a sign of early improvement

Class III: K⁺ channel blockers and multimechanism (Continued)

Ibutilide ^{82,131,132} (mat only, IV only)	LD: for acute termination of drug-refractory atrial tachyarrhythmia: <60 kg = 0.01 mg/kg IV over 10 min, may repeat after 10 min >60 kg = 1 mg IV over 10 min, may repeat after 10 min	NA	QT prolongation, TdP, hold other QT prolonging drugs before and after; telemetry for at least 4 h post-infusion	Embryotoxic, teratogenic, avoid in first trimester
Dronedarone	Contraindicated in pregnancy			Fetal harm from visceral and skeletal malformations in animal studies

Class IV: Calcium channel blockers

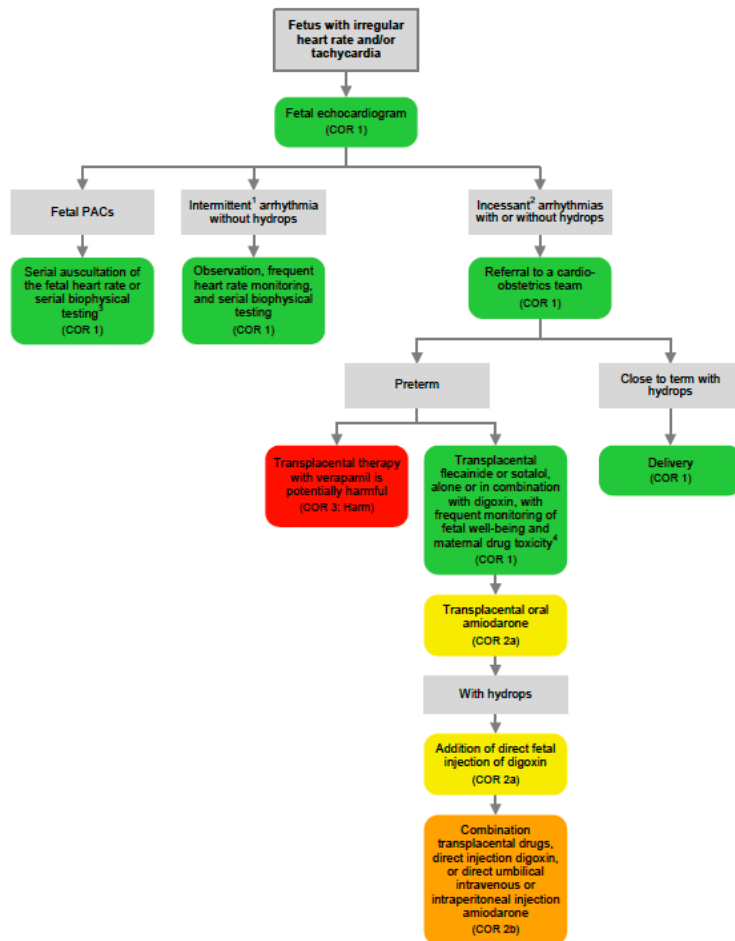
Verapamil ¹³³ (mat only IV, PO)	LD: 5-10 mg IV, can repeat after 30 min MD: 120-480 mg/day PO	125-400 µg/mL	(Substitute with adenosine or beta-blocker if possible) mat hypotension, uterine muscle relaxant	Embryotoxic, fetal bradycardia, fetal hypoxia Infant: hypotension, hypocontractility, fetal demise, jaundice, seizures, hematologic abnormalities; Concentrates in breast milk
Diltiazem ⁸³ (mat only IV, PO)	LD: 0.25 mg/kg IV over 2 min, repeat 0.35 mg/kg, then 5-15 mg/h IV infusion (start immediately after bolus) MD: XR 180-360 mg PO Q day	50-200 ng/mL	CNS+ +, potent vasodilator+ +, hypotension, bradycardia, uterine muscle relaxant	Embryotoxic, fetal demise, hypocontractility, M/F serum:breast milk = 1:1

Other arrhythmia drugs

Adenosine ²⁵ (mat IV)	LD: 6-12 mg rapid IV, up to 24 mg has been used	NA	Flushing, transient chest pain and bradycardia	Safe for fetus when mother is treated IV; not useful for treatment of fetal SVT Intracordal: nonsustaining cardioversion, fetal demise
Atropine (mat IV)	LD: 0.02 mg/kg IV, repeat Q 3-5 min for cardiac arrest (max 3 mg), lower doses for acute 2:1 AV block	Not used	Rebound sinus tachycardia; improvements in AV conduction may be transient	F/M ratio 0.13
Magnesium sulfate ¹³⁴ (mat/fetal IV, then PO)	LD: 2-6 g IV over 20 min MD: 1-2 g/h; treatment for >48 h is generally avoided though may consider redosing if VT recurs; PO 200-600 mg/day	<6 mEq/L; monitor elbow and patellar reflexes	GI+ +, fatigue+ +, CNS+ + symptoms; STOP for loss of patellar reflex and/or levels >6 mEq/L; levels >5 mEq/L associated with maternal ECG changes and proarrhythmia	Hypotonia+ , lower assigned Apgar scores

*The PDR (Prescriber's Digital Reference) website (<https://www.pdr.net/>) is an additional resource; the information provided may vary from the PDR based on other evidence for antiarrhythmic drug use during pregnancy and lactation.

†Dosages may vary from those listed in the Food and Drug Administration–approved labeling (available at <https://dailymed.nlm.nih.gov/dailymed/>) and are not meant to replace clinical judgment. Drug doses provided here can be used for either maternal or fetal treatment. Maternal use, fetal use, or both are noted in the first column along with the routes available. Treatment during pregnancy requires a strong knowledge of pregnancy pharmacokinetics and is best done by the cardio-obstetrics team. The lowest effective drug dose should be used, but higher drug doses may be required during the latter part of pregnancy to maintain therapeutic serum concentrations. In general, all of these drugs are started during a hospital stay. When intravenous drugs are used, telemetry, electrocardiogram (ECG), and blood pressure monitoring are important. For chronic outpatient administration, consider long-acting preparations if available. Transplacental drug treatment does not necessarily require continuation of the drug until delivery and does not mandate the need for neonatal drug therapy.
+++ : very common, ++ : common, + : occasional, AFL: atrial flutter, AV: atrioventricular, CNS: central nervous system, DFT: direct fetal therapy, F: fetal, GA: gestational age, GI: gastrointestinal, HTN: hypertension, IC: intracordal, IM: intramuscular, IV: intravenous, LD: loading dose, LQTS: long QT syndrome, M or Mat: maternal, MD: maintenance dose, NA: not applicable, N/V: nausea and vomiting, PO: by mouth, proarrhythmia: worsening of an arrhythmia as the result of treatment, QTc: corrected QT interval, SHD: structural heart disease, SVT: supraventricular tachycardia, SR: sustained-release, TdP: torsades de pointes, WPW: Wolff-Parkinson-White syndrome, VT: ventricular tachycardia.



Management of fetuses with irregular heart rate and tachycardia.

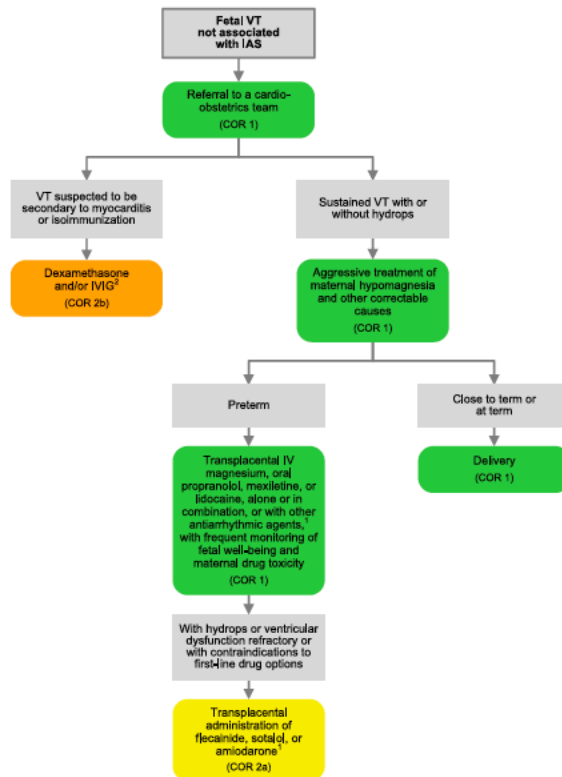
¹Intermittent is defined as, 50% of the time.

²Incessant is defined as, 50% of the time.

³If these are unavailable, nonstress testing is recommended.

⁴Drug selection according to the specific arrhythmia mechanism. The term close to term is purposely vague, but it implies likely viability after delivery.

PAC: premature atrial contraction.

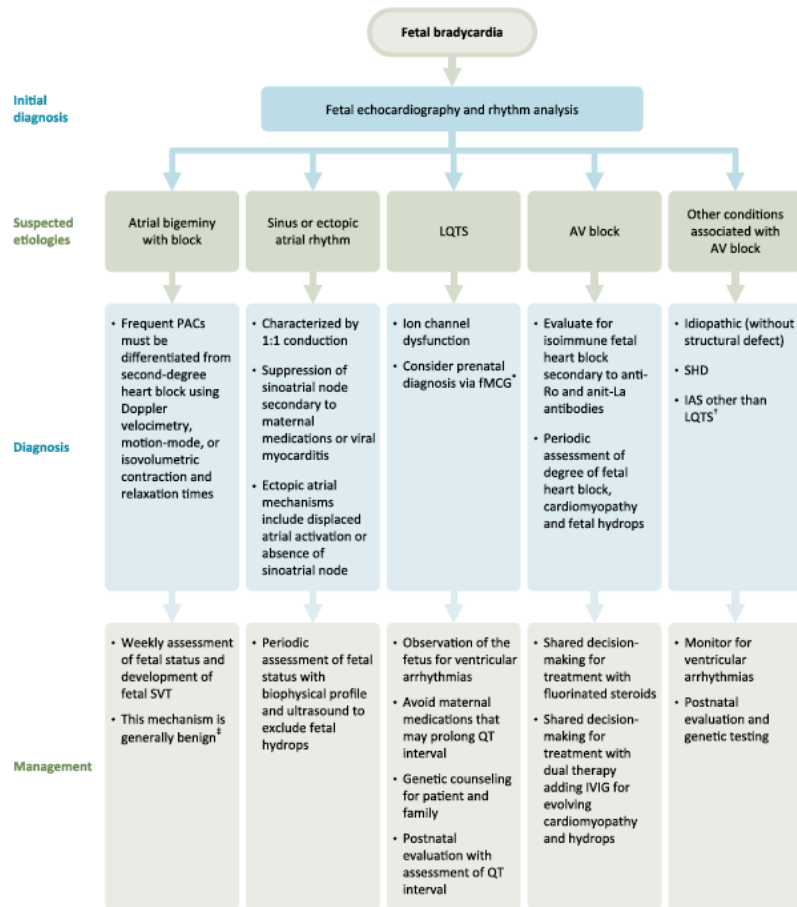


Algorithm for management of ventricular tachycardia (VT) in the fetus not secondary to inherited arrhythmia syndrome (IAS).

1Choice of drug according to the arrhythmic etiology and/or underlying maternal-fetal substrate.

2Depending on gestational age. The term close to term is purposely vague, but it implies likely viability after delivery.

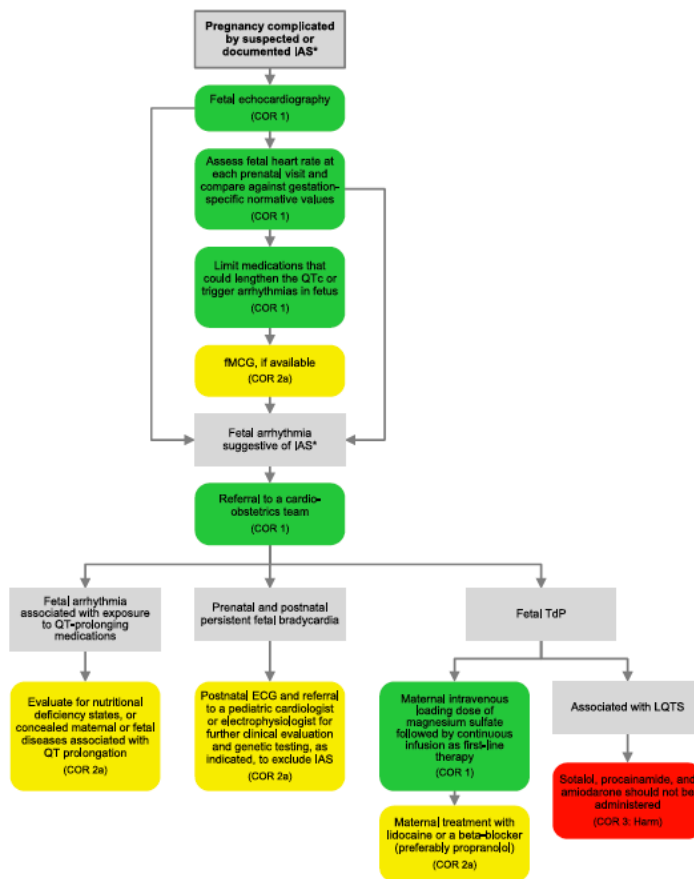
IV: intravenous, IVIG: intravenous immunoglobulin.



Diagnosis and management of fetal bradycardia.

Please delete * † ‡

AV: atrioventricular, fMCG : fetal magnetocardiography, IAS : inherited arrhythmia syndromes, IVIG : intravenous immunoglobulin, LQTS: long QT syndrome, PAC: premature atrial contraction, SHD: structural heart disease.



Management of the fetus in pregnancies complicated by potential or documented inherited arrhythmia syndrome (IAS).

*Long QT syndrome (LQTS) is the most common IAS setting in which fetuses manifest arrhythmias.

ECG: electrocardiogram, fMCG: fetal magnetocardiography, QTc: corrected QT interval, TdP: torsades de pointes.

2023 HRS expert consensus statement on the management of arrhythmias during pregnancy. *Heart Rhythm*. 2023;20:e175-e264.