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Diagnosis and management of arrhythmias in pregnancy

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Abstract

Background: Arrhythmias are the most common cardiac complications occurring in pregnancy. Although atrial or ventricular premature complexes may explain the majority of palpitations in pregnancy, the full spectrum of arrhythmias can occur.

Main body: This article summarizes the evaluation and management of arrhythmias in pregnancy. Hemodynamically unstable arrhythmias need urgent cardioversion. For mild cases of benign arrhythmia, treatment is usually not required. Symptomatic but hemodynamically stable arrhythmic patients should first undergo an evaluation to establish the type of arrhythmia and the presence of structural heart disease. Given the potential risks of antiarrhythmic pharmacotherapy in pregnancy, this will ultimately determine the necessity for treatment. We will discuss the main antiarrhythmic medications, which have some established evidence of safety in pregnancy.

Conclusions: In hemodynamically stable pregnant patients with A.F. or AFL with rapid ventricular rates (RVR), I.V. beta-blockers are recommended as the first-line option, and digoxin or verapamil, alone or in combination are recommended as second-line options for initial rate control in the absence of preexcitation.

Keywords: Antiarrhythmic; Atrial fibrillation; Bradyarrhythmia; Fetal arrhythmia; Inherited arrhythmia syndrome; Maternal arrhythmia; Pregnancy; Supraventricular tachycardia; Ventricular tachycardia

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

Background: Physiological, hormonal, and autonomic changes related to arrhythmogenesis

Hemodynamic changes in pregnancy: Arrhythmias among pregnancy-related hospitalizations: The most frequent arrhythmia diagnosis was sinus arrhythmia (60% of the diagnoses, 104 per 100,000 pregnancy-related hospitalizations), followed by atrial or ventricular extrasystole (19%) and paroxysmal supraventricular tachycardia (PSVT) (14%). Atrial fibrillation (AF) and atrial flutter (AFL) (1%), ventricular fibrillation (VF) (1%), and high-degree atrioventricular (AV) block (1%)were rarely diagnosed. The rate of mortality from arrhythmias decreased to 3.7%. [1-12]

Pregnancy may aggravate preexisting arrhythmias, especially in older women (199 per 100,000 at 41-50 vs. 55 per 100,000 at 18-30) and women with CHD. In the 1321 women enrolled in ROPAC (Registry Of Pregnancy And Cardiac Disease), 17 (1.3%) had AF or AFL, with a higher incidence (2.5%) noted in women with mitral valve disease [5].

Main text:

Types of arrhythmias during pregnancy:

Inappropriate sinus tachycardia (IST) (defined as a resting heart rate >100, a mean ambulatory heart rate >90, and associated symptoms). Aside from symptoms, IST has not been associated with adverse long-term outcomes [7].

Recurrence rates during pregnancy in patients with a history of SVT, paroxysmal AF/AFL, and VT were 50%, 52%, and 27%, respectively.

-Management of syncope and orthostatic hypotension in the pregnant patient:

Syncope is a sudden, transient loss of consciousness due to global cerebral hypoperfusion.

The overall incidence of syncope during pregnancy was 1% (9.7/1000 pregnancies) [8].

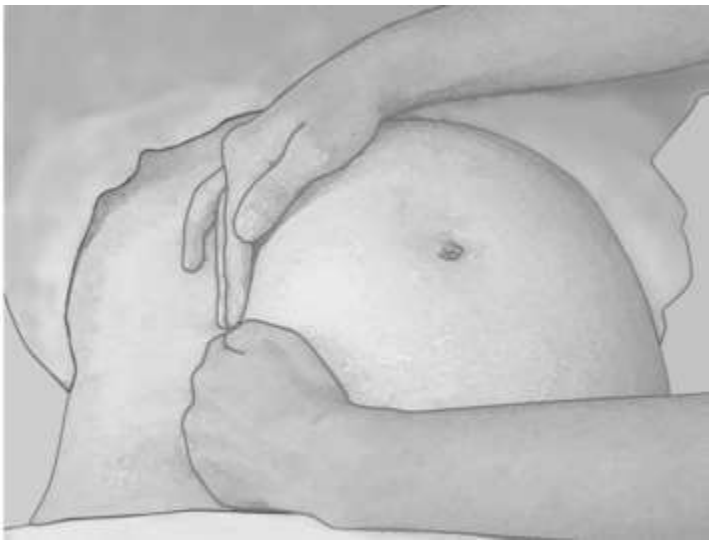
A supine hypotensive syndrome is unique to pregnancy; 8% to 11% of women develop greater than 30%, or 30 mmHg, systolic blood pressure drop with or without symptoms when lying supine [8].

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

The gravid uterus begins to compress the inferior vena cava in the supine position, starting at the 20th week of pregnancy, with severe obstruction at term.

The pregnant patient's left tilt of ≥30 degrees or left lateral position increases the inferior vena cava volume and cardiac output significantly compared with the prone position [Fig. 1].

Figure 1. Manual leftward and upward uterine displacement



The most frequent type of syncope occurring during pregnancy is reflex-mediated vasovagal syncope.

The prevalence of syncope in pregnancy due to orthostatic hypotension is unknown. Still, it may occur in patients with volume depletion due to severe bleeding or vomiting or in patients taking medications for an underlying SHD.

Blood pressure measurement in supine, sitting, and standing positions, with a detailed history taking, should point to the diagnosis in these patients. Sudden fast palpitations starting before syncope, preexisting diagnosis of tachyarrhythmias, underlying congenital or SHD or channelopathy, and family history of premature death or arrhythmias should raise suspicion of underlying cardiac etiology. Detailed physical examination and 12-lead electrocardiogram (ECG) should further help in the differential diagnosis.

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

Pregnancy-induced increases in estradiol, progesterone, and free cortisol may also predispose pregnant patients to cardiac arrhythmias. As pregnancy progresses, there is a shift from a vagal to a higher sympathetic milieu, resulting in an increase in basal heart rate of 10 to 20 beats per minute (bpm).[8]

Antiarrhythmic drugs use during pregnancy:

General considerations for antiarrhythmic drugs in pregnancy (Tables 1, 2)

Table 1. Table of antiarrhythmic drugs for use in pregnancy

Drug	Therapeutic maternal dose range	Toxicity/adverse events	
		Maternal	**Fetal/neonatal**
Digoxin	**LD:** 1.5-2.0 mg/24 h PO/IV divided Q 8 h **MD:** 0.125-0.5 mg/day PO, divided BID	N/V+++, anorexia++, sinus bradycardia+ or Mobitz I AV block+, proarrhythmia +, avoid in WPW	Infant: Usually well tolerated, often used in combination, vomiting++, sinus bradycardia++, AV block, proarrhythmia
Class IA: Na+ channel blockers			
Procainamide	**LD:** 15 mg/kg IV over 30 min **MD:** 1-4 mg/min infusion	N/V+, TdP, ↑QTc, IV, uterine irritability, preterm labor	
Quinidine gluconate	**LD:** 200-400 mg PO Q 2-3 h until therapeutic effect (max three g/day) **MD:** XR 324-648 mg Q 8-12 h	N/V+++, CNS+, ↑QTc+, proarrhythmia, TdP	
Class IB: Na+ channel blockers			
Lidocaine	**LD:** 1-1.5 mg/kg LD IV, 300 mg max **MD:** infusion of 1-4 mg/min	N/V++, CNS+, proarrhythmia	CNS++, bradycardia
Mexiletine	**LD:** 3-5 mg/kg IV at 0.25 mg/kg/min (up to 10 mg) **MD:** 200-300 mg TID		
Class IC: Na+ channel blockers			

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

Flecainide	**MD:** 200-400 mg/day divided Q 8-12 h PO, Avoid in SHD	Visual/CNS++, mild P/QRS widening + and widening with longer1 ° AV block+, ↑QTc, AFL	Fetal/neonatal QRS
Propafenone	**MD:** 150 mg Q 8 h, increase slowly (max 900 mg/day), extended-release 225-425 Q 12 h PO Avoid in SHD	CNS++, ↑QTc, GI+, QRS widening, AFL, bradycardia	
Class II: Beta-blockers			
Propranolol	**MD:** 60-320 mg/day divided Q 6-12 h	Fatigue++, bradycardia++, hypotension++, AV block, ↑uterine tone	
Class III: K+ channel blockers and multi-mechanism			
Sotalol	**MD**: 160-320 mg/day divided BID or Q 8 h	N/V/fatigue/CNS++, sinus bradycardia+, ↑QTc (hold or reduce dose if QTc >500 ms, proarrhythmia	CNS, +/- proarrhythmia, bradycardia+, rare ↑QTc; well tolerated in infants
Amiodarone	**LD:** 1800 mg/day PO divided Q6 h × 48 h; lower LD (1200 mg) if concurrent drug therapy. Maternal parenteral LD: 1000 mg over 24 has 150 mg/10 min, then 360 mg/6 h, then 540 mg/18 h IV **MD:** 600 mg × 1 wk, then 200- 400 mg/day;	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	↑thyroid++, fetal TdP If given for LQTS, goiter, neurodevelopmental concerns
Dronedarone	Contraindicated in Pregnancy		
Class IV: Calcium channel blockers			

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

Verapamil	**LD:** 5-10 mg IV, can Repeat after 30 min **MD:** 120-480 mg/day PO	(Substitute with adenosine or beta-blocker if possible) mat hypotension, uterine muscle relaxant	Embryotoxic, fetal bradycardia, fetal hypoxia

Other arrhythmia drugs			
Adenosine	**LD:** 6-12 mg rapid IV,	Flushing, transient chest pain, and bradycardia	
Atropine	**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.	Rebound sinus tachycardia; improvements in AV conduction may be transient.	
Magnesium sulfate	**LD:** 2-6 g IV over 20 min **MD:** 1-2 g/h;	GI++, fatigue++, CNS++ symptoms;	

LD = loading dose, MD = maintenance dose, N/V = nausea and vomiting, GI = gastrointestinal

The use of antiarrhythmic drugs in pregnancy requires attention to potential changes in pharmacokinetics due to changes in maternal physiology, such as metabolism and an increase in intravascular volume [9-10].

Table 1. Table of antiarrhythmic drugs for use in pregnancy

Table 2. Antiarrhythmic drug safety for commonly used drugs in pregnancy [1].
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	Propranolol	Metoprolol	Nadolol	Atenolol	Mexiletine	Quinidine	Sotalol
Use during pregnancy	Safe	Safe	Safe	Risk	Caution	Safe	Safe
Use when breastfeeding	Safe	Safe	Caution	Risk	Caution	Safe	Safe

Table 2. Antiarrhythmic drug safety for commonly used drugs in pregnancy [1].

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

- **Physiological, hormonal, and autonomic changes related to arrhythmogenesis:**

Pregnancy-induced cardiovascular changes (including increased resting heart rate, increased blood volume resulting in cardiac chamber dilation with greater end-diastolic volumes, and higher levels of placental-originated potentially arrhythmogenic hormones) may predispose pregnant patients to cardiac arrhythmias.

Duan et al [13] and Grewal et al.[14] reported the birth weight reduction associated with beta-blockers to be less than 200 grams, therefore not of great clinical consequence in most instances. Thus, in the setting of potentially life-threatening scenarios(e.g., some inherited arrhythmia syndromes [IAS]), a maternal indication for prescription of a beta-blocker takes priority over potential fetal growth-restriction concerns, and beta-blocker therapy should continue during pregnancy and the postpartum period.

- **Recommendations for general electrophysiological management** [15-24]

1. In pregnant patients with cardiac arrhythmias, treatment should be maintained e during the pregnancy, delivery, and postpartum periods, using drugs with the most extended data of safe use and efficacy in pregnancy, at the lowest effective dose, and with periodic evaluation for the persistence of medications.

In general, the approach to evaluating arrhythmias in pregnant patients is similar to that inpatients who are not pregnant, as the primary goal is to optimize treatment for the mother without compromising fetal safety.

- **Recommendations for team-based care and shared decision-making:**

1. For the current management and treatment of pregnant patients with cardiac arrhythmias, a cardio-obstetrics team, a cardiologist, and an electrophysiologist, when fetal arrhythmias are present, an anesthesiologist should be engaged in optimal management and birth strategies.

- **Procedures for arrhythmia management during pregnancy:**

- Figure 2. Cardioversion during pregnancy [20]

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

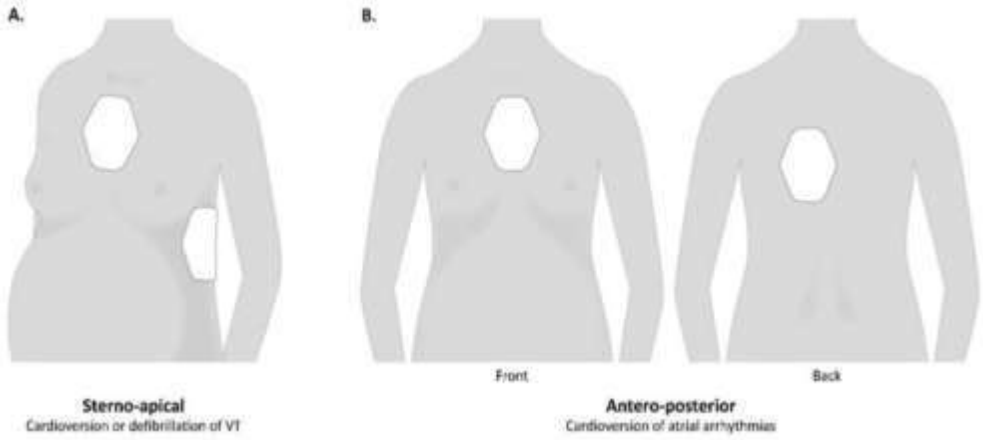
1. In pregnant patients with unstable SVT or VT, direct current cardioversion or defibrillation is recommended with energy dosing, as in the nonpregnant patient.
2. In pregnant patients with stable, symptomatic SVT or VT refractory or with contraindications to pharmacological therapy, elective synchronized cardioversion is advised with fetal evaluation by the cardio-obstetrics team.
3. In pregnant patients undergoing synchronized cardioversion or defibrillation, electrode placement should avoid breast tissues [Fig 2].

- **Radiation exposure during cardiac procedures and hemodynamic concerns related to pregnancy** [20]:

1. In pregnant patients with hemodynamically significant sustained cardiac arrhythmias refractory or with contraindications to drug therapy who are applicable for catheter ablation, the benefit of controlling maternal tachycardia by ablation should supersede the potential radiation risks to the fetus, especially if the procedure is done after the first trimester and radiation exposure is minimized [20-23].
2. In pregnant patients undergoing catheter ablation, techniques are recommended to minimize radiation exposure to as low as possible during the procedure [24].
3. In pregnant patients undergoing cardiac procedures requiring fluoroscopy, placing a pelvic lead apron over the patient is not beneficial because it does not substantially reduce radiation exposure to the fetus.

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

Figure 2. Electrode placements during pregnancy to avoid breast tissue



- **Anesthesia considerations:**

1. In pregnant patients with arrhythmias associated with hemodynamic instability requiring cardiac interventions, general anesthesia is recommended in preference to regional anesthesia for a secure airway and improved oxygenation during hemodynamic instability.
2. Aortocaval compression occurs due to the enlarging uteroplacental unit as early as the second trimester of pregnancy [2]. More contemporary cardiac MRI data corroborate this pregnancy phenomenon, demonstrating improved cardiac function with the left lateral tilt of 30 degrees, compared with parameters obtained in the supine position. Left lateral manual uterine displacement can be performed if the supine position of the thorax is preferred or required to facilitate interventions [1]
3. Medications used throughout the anesthesia process may exacerbate the arrhythmogenic potential of the underlying substrate, such as prolongation of the QT interval

- Perioperative medications that prolong the QT interval

Quinolones, macrolides, Terfenadine, diphenhydramine Famotidine, Benzodiazepines (except midazolam, Ketamine, thiopental, Edrophonium, neostigmine, glycopyrrolate, Methadone, sufentanil, Epinephrine, norepinephrine, dobutamine,
dopamine, isoproterenol [18].

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

- **Delivery and lactation:**

1. In pregnant patients with cardiac arrhythmias, the route of delivery (vaginal or cesarean) should be determined by the obstetrical factors along with the continuation of antiarrhythmic drug therapy.
2. Pregnant patients receiving antiarrhythmic drug therapy should receive adequate pain control during labor, ideally using epidural anesthesia, to avoid pain-induced catecholamine increase that may trigger preexisting arrhythmias.

- **Diagnosis of pregnant patients with palpitations:**

1. Pregnant patients presenting with modest sinus tachycardia or extrasystoles without suspicion of underlying cardiopulmonary disease should be reassured.
2. In pregnant patients presenting with palpitations, a detailed history, physical examination, resting 12-lead ECG, and related blood testing should be performed at the initial evaluation.

Recommendations for arrhythmia management of the pregnant patient with structural Heart disease (SHD):

1. Patients with SHD and a history of arrhythmias contemplating pregnancy should have preconception counseling.

2. Pregnant patients who present with new complex SVT or VT should undergo an evaluation for SHD.

- **Arrhythmia management in the pregnant patient with congenital heart disease** [20]

1. Patients with CHD and arrhythmias considering pregnancy should receive preconception counseling, with input from an adult congenital cardiologist with expertise in adult CHD, to determine maternal cardiac, obstetric, and fetal risks.

2. Patients contemplating pregnancy with Fontan circulation and refractory arrhythmias should be advised that pregnancy is potentially harmful.

- While amiodarone is an effective antiarrhythmic for many arrhythmias, it is associated with a risk of fetal abnormalities. Up to 17% of neonates may develop hypothyroidism and some evidence of neurotoxicity [22-26]. Thus, amiodarone is generally limited to instances of refractory or life-threatening arrhythmias that cannot be controlled with other medications and require close monitoring for possible

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

side effects—shared decision-making with the mother before therapy initiation, discussing potential long-term risks to the mother and fetus.

- **Arrhythmia management in pregnant patients with valvular heart disease:**

. In pregnant patients with mitral stenosis and acute onset of either AF or AFL of any duration, synchronized cardioversion is recommended, as long as the patient is adequately anticoagulated or atrial thrombus is excluded, and subsequent anticoagulation will be provided with the course as in the nonpregnant patient.

3. Therapeutic anticoagulation is recommended throughout pregnancy unless there is a contraindication in pregnant patients. Note: an AF during pregnancy should receive anticoagulants, whatever the Chad-vasc score.

-**Arrhythmia management in pregnant patients with arrhythmogenic cardiomyopathy** [16]

. Pregnant patients with ACM should be treated for documented or potential arrhythmias as in the nonpregnant patient, including continuation of beta-blockers and antiarrhythmic drugs, favoring options with the best record of safety during pregnancy.

- **Arrhythmia management in the pregnant patient with hypertrophic cardiomyopathy** [22]

. Pregnant patients with HCM should be treated for documented or potential arrhythmias as in the nonpregnant patient, including continuation of beta-blockers and the use of antiarrhythmic drug–and device-based therapies as needed, favoring options with the best record of safety in pregnancy.

Management of fetal arrhythmias [7-18, 21]

1. Fetuses with intermittent AFL or intermittent SVT (defined as tachycardia <50% of the time) and no hydrops should be managed with observation and frequent fetal heart rate monitoring (auscultation), ideally under the guidance of a cardio-obstetrics team.
2. Fetuses with incessant SVT or AFL with or without hydrops who are not considered to be mature enough for delivery should be treated transplacentally with flecainide or sotalol, alone or in combination with digoxin, with frequent monitoring of fetal well-being and maternal drug toxicity,

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

and with drug selection according to the specific arrhythmia mechanism.

3. Fetal ventricular arrhythmias not associated with inherited arrhythmia syndromes [14-18]
   Fetuses with sustained VT with or without hydrops who are not considered to be mature enough for delivery should be treated transplacentally with either intravenous magnesium or oral propranolol, mexiletine, or lidocaine, alone or in combination, or with other antiarrhythmic agents according to the specific arrhythmia etiology, with frequent monitoring of fetal well-being and maternal drug toxicity.

- **Management of fetal bradycardia conduction system disorders** [10]
- In pregnancies complicated by third-degree fetal heart block, echocardiographic monitoring is recommended to monitor fetal hydrops and cardiomyopathy since these conditions can lead to fetal compromise or the need for delivery.
- In pregnant patients with positive anti-Ro and anti-La antibodies, periodic echocardiographic monitoring for developing immune heart block and immune fetal cardiomyopathy is reasonable.

- Inherited arrhythmia syndromes.

- Management and risk stratification of inherited arrhythmia syndromes during pregnancy [15]

1. In a pregnant patient with an IAS (inherited arrhythmia syndrome) and presumed cardiac syncope or documented VT, referral to an electrophysiologist is recommended to consider therapeutic interventions, escalation of pharmacological therapy, and possible ICD implantation.

- **Management of long QT syndrome in pregnancy**

1. In pregnant patients with LQTS and a preconception indication for beta-blocker therapy, beta-blockers should be continued throughout pregnancy, delivery, and the postpartum period, including breastfeeding [18].
2. In pregnant patients with LQTS who experience cardiac arrest in pregnancy or in whom cardiac syncope or ventricular arrhythmias occur despite beta-blocker use, intensification of therapy, including ICD implantation, if indicated, is recommended as in the nonpregnant patient [1,18].

- **Management of Brugada syndrome in pregnancy:**

. In pregnant and postpartum breastfeeding patients with BrS, education about the prompt treatment of

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

fever, such as in cases of mastitis with antipyretics, is recommended, as fever is a potential precipitant for sudden death [6, 14].

- **Management of catecholaminergic polymorphic ventricular tachycardia in pregnancy** In pregnant patients with CPVT, with symptoms despite beta-blocker therapy, such as recurrent syncope, VT, or cardiac arrest, maximization of treatment with the addition of flecainide and an ICD is recommended as in the nonpregnant patient [16].

- **Management of inherited arrhythmia syndromes *in the fetus*:**

- long QT syndrome: In fetuses with TdP, a maternal intravenous loading dose of magnesium sulfate followed by continuous infusion should be administered as first-line therapy at all stages of pregnancy before considering urgent delivery [2].

The Food and Drug Administration has replaced the ABCDX classification system for labeling the safety of medications during pregnancy with a narrative labeling system. The Pregnancy and Lactation Labeling Rule (PLLR) is intended to provide more information about available data, clinical considerations, and differences in degrees of fetal risk [26].

Conclusions, summary and future directions

- Most palpitations in Pregnancy are benign and usually occur due to atrial or ventricular premature complexes. Careful consideration should be given to the gestation stage and the patient's hemodynamic state.
- In hemodynamically stable pregnant patients with acute onset of SVT, intravenous adenosine is recommended as the first-line pharmacological therapy.
- In pregnant patients with symptomatic SVT without preexcitation, metoprolol, propranolol, and digoxin should be used as first-line options, and verapamil as the second-line option for the chronic oral prophylaxis of SVT.
- In hemodynamically stable pregnant patients with A.F. or AFL with rapid ventricular rates (RVR), I.V. beta-blockers are recommended as the first-line option, and digoxin or verapamil, alone or in combination are recommended as second-line options for initial rate control in the absence of preexcitation.

ISSN:0975-3583,0976-2833 VOL15,ISSUE07,2024

- In pregnant patients with A.F. or AFL with persistent symptoms or RVR refractory, elective direct current cardioversion is recommended with anticoagulation as in nonpregnant patients.
- In pregnant patients with A.F. or AFL with continued symptoms or RVR despite rate control therapy, flecainide in the absence of structural heart disease (SHD) or sotalol in the absence of severe LV dysfunction is reasonable.
- The choice of anticoagulation, namely low molecular weight heparin (LWMH) or vitamin K antagonists (i.e., warfarin), depends on the stage of gestation. Direct oral anticoagulants (DOACs) are contraindicated altogether.
- Direct current cardioversion is recommended in pregnant patients with sustained V.T. and hemodynamic compromise.
- In pregnant patients with idiopathic V.T. and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract V.T. and intravenous verapamil for fascicular V.T. are recommended as first-line options.
- In pregnant patients with recurrent V.T. refractory or contraindications to beta-blockers requiring additional antiarrhythmic drug therapy, treatment with flecainide, sotalol, or mexiletine is recommended.

List of Abbreviations

ACM = arrhythmogenic cardiomyopathy; AF = atrial fibrillation; AFL = atrial flutter; AV = atrioventricular; BLS = basic life support; beats per minute = bpm; BrS = Brugada syndrome; CHD = congenital heart disease; CPR = cardiopulmonary resuscitation; CPVT = catecholaminergic polymorphic ventricular tachycardia; ECG = electrocardiogram; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; IAS = inherited arrhythmia syndrome; ICD = implantable cardioverter defibrillator; ICM = implantable cardiac monitor; IST = inappropriate sinus tachycardia; LQTS = long QT syndrome; LV = left ventricular; PAC = premature atrial contraction; PSVT = paroxysmal supraventricular tachycardia; PVC = premature ventricular contraction, QTc = corrected QT interval; RVR = rapid ventricular rate; SHD = structural heart disease; SVT = supraventricular tachycardia; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia

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Figure legends

Figure 1. Manual leftward and upward uterine displacement

Figure 2. Electrode placements during pregnancy to avoid breast tissue

Declaration

Ethical Compliance with Human Study: This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration

Ethical approval and consent to participate: This review is approved by the ethical office of our Faculty of Medicine. No patients to give consent for inclusion.

Consent for publication: All authors consent for publishing the review

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Ethical Guidelines: The review follow the ethical guidelines of this subject. Availability of data and materials: Data are in the references.

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Contribution: SR: was involved in writing the paper and submitting it.

AA: Revised the paper

AM: Revised the paper

All authors contributed to the script—original draft preparation and approved the final version.

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Institutional Review Board Approval (IRB Approval, add in the Methods section)

The Ethical Committee of the Faculty of Medicine Alexandria University approved the review article.

- **Data Availability**

Data and master charts are available with Dr. SR.

Ethical Compliance with Human Study: This review article was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration

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