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Catarina Sofia Neves Graça Nogueira Pinto

Arritmias na Gravidez

Pregnancy Cardiac Arrhythmias

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Arritmias na Gravidez

Pregnancy Cardiac Arrhythmias

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Index

Abstract

Cardiac arrhythmias during pregnancy are common and a cause of concern for the mother and the fetus wellbeing, although the majority is benign and not associated with cardiac structural disease. The aim of this review is to summarize physiological changes during pregnancy and their influence on arrhythmias development; identify the most common arrhythmias during this period, their impact on maternal and neonatal outcomes and their management. The most common arrhythmias during pregnancy seem to be sinus tachycardia, sinus bradycardia or sinus arrhythmia (104 episodes/100000 pregnancies). Luckily, ventricular tachycardia is rare in healthy women without underlying organic heart disease, having polymorphic ventricular tachycardia a high risk of degenerating into ventricular fibrillation. Pregnancy related physiological changes may contribute for a sustained arrhythmia, so, besides palpitations being frequent during pregnancy, a careful patient assessment is needed. Adverse outcomes were described such as a higher diagnosis rate of intrauterine growth restriction and placental abruption. Life-threatening rhythm disorders in women of childbearing age are relatively rare and treatment should be reserved for hemodynamically unstable arrhythmias or for those causing debilitating symptoms. The use of antiarrhythmic drugs during this phase is a challenge due to their potential adverse effects and potential teratogenicity, since the majority crosses the placental barrier in some extent, being categorized in Food and Drug Administration class C. Some cases of unstable ventricular arrhythmias and of high risk of sudden cardiac death might need an implantable cardioverter-defibrillator.

Key-Words

Pregnancy cardiac arrhythmias; Tachycardia; Bradycardia; Antiarrhythmic drugs; Maternal and neonatal outcomes; Implantable cardioverter-defibrillator.

Resumo

As arritmias cardíacas durante a gravidez são comuns e uma causa de preocupação para o bem-estar materno e fetal, embora a maioria seja benigna e não associada a doença cardíaca estrutural. O objetivo desta revisão é sistematizar as alterações fisiológicas que ocorrem durante a gravidez e a sua influência no desenvolvimento de arritmias; identificar as arritmias mais comuns durante este período, o seu impacto na saúde materna e neonatal e a sua abordagem e tratamento. As arritmias mais comuns durante a gravidez são a taquicardia sinusal, a bradicardia sinusal e a arritmia sinusal (104 episódios/100000 gravidezes). Felizmente, a taquicardia ventricular é rara em mulheres saudáveis sem doença cardíaca estrutural subjacente, tendo a taquicardia ventricular polimórfica um elevado risco de degenerar em fibrilhação ventricular. As alterações fisiológicas verificadas poderão contribuir para uma arritmia sustentada, pelo que, apesar das palpitações serem frequentes durante este período, é necessária uma avaliação cuidadosa da paciente. Resultados adversos estão descritos, como uma maior taxa de restrição do crescimento intra-uterino e de placenta abrupta. Alterações do ritmo potencialmente fatais são raras durante a idade fértil, estando o tratamento reservado para arritmias hemodinamicamente instáveis ou para aquelas causadoras de sintomas debilitantes. O uso de fármacos antiarrítmicos é um desafio pelos seus potenciais efeitos adversos e teratogenicidade, pois a maioria atravessa a barreira placentária em alguma extensão, sendo categorizados em classe C pela Food and Drug Administration. Casos de arritmias ventriculares instáveis ou com alto risco de morte súbita poderão ter indicação para a implantação de um cardioversor-desfibrilhador.

Palavras-chave

Arritmias na gravidez; Taquicardia; Bradicardia; Fármacos antiarrítmicos; Outcomes maternos e neonatais; Cardioversor-desfibrilhador implantável.

List of Abbreviations	
AF	Atrial fibrillation
ASD	Atrial septal defect
AV	Atrioventricular
AVNRT	Atrioventricular nodal re-entrant tachycardia
CNS	Central nervous system
CO	Cardiac output
ECG	Electrocardiogram
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GDM	Gestational diabetes mellitus
Hb	Haemoglobin
HR	Heart rate
ICD	Implantable cardioverter-defibrillator
ICU	Intensive Care Unit
IUFD	Intrauterine fetal demise
IUGR	Intrauterine growth restriction
IV	Intravenous
LMWH	Low molecular weight heparin
LQTS	Long QT syndrome
LV	Left ventricular
LVEDD	Left ventricular end diastolic diameter
NICU	Neonatal Intensive Care Unit
NYHA	New York Heart Association
PHTN	Pregnancy-induced hypertension
PROM	Premature rupture of membranes
SGA	Small for gestational age
SV	Systolic volume
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
VSD	Ventricular septal defect
VT	Ventricular tachycardias
WPW	Wolf-Parkinson-White

Methods

For this narrative review research three databases were used Pubmed, Web of Science and Scopus with the following search terms “arrhythmias during pregnancy”, “arrhythmias and pregnancy”, “atrial fibrillation and pregnancy”, “cardiac alterations during pregnancy”, “physiological cardiac changes in pregnancy”, “pregnancy in women with an implantable cardioverter-defibrillator” and “implantable cardioverter-defibrillators effects on pregnancy”. The articles chosen were those in english and after a careful reading of their abstract, without restriction of the type of article or year of publishing. References were searched for additional relevant articles.

Introduction

Arrhythmias during pregnancy are frequent and may disturb mother and fetus wellbeing,[1] being their risk relatively higher during labour and delivery.[2,3] Some can be a recurrence of a previous diagnosed arrhythmia, others the first presentation of a known structural heart disease.[1] However, mostly, there’s no previous history of heart disease.[1] Simultaneously, most of these arrhythmias in young women is benign and not associated with cardiac structural disease, only a minority of cases will need antiarrhythmic drugs,[1,2,4] and many inherent rhythm disorders manifest before childbearing age.[5]

In pregnancy, palpitations are common; heart rate (HR) increases by 25% physiologically, sinus tachycardia, particularly during third trimester, is not uncommon, and ectopic beats and non-sustained arrhythmia are encountered in more than 50% of pregnant women.[1]

History of structural heart disease, exacerbating situations, exercise capacity, description of arrhythmia onset and termination and any associated symptoms, especially syncope, should be sought. Family history of sudden death or structural heart disease is important. In the electrocardiogram (ECG), electrical axis can be displaced slightly due to cardiac rotation resulting from the gravid uterus, but tends to remain within the normal range and the PR, QRS

and QT intervals could be shortened without clinical implications. Other more obvious changes should be regarded as abnormal and investigated.[6]

Greater arrhythmia occurrence rates might be expectable, since many women are now delaying pregnancy until later in life, adding potential effects of degenerative cardiovascular disease and associated disease (hypertension, adult onset diabetes, atherosclerotic vascular disease and chronic kidney disease).[5,7]

Cordina et al (2010),[6] quoting other authors, stated that in retrospective studies only 0.17% of hospital admissions during pregnancy were for cardiac arrhythmia; for every 100000 pregnant women, 24 will be admitted for management of supraventricular tachycardia (SVT), two with atrial fibrillation (AF), two with ventricular tachycardia (VT) or fibrillation and 1.5 with atrioventricular (AV) block; arrhythmias of haemodynamic significance during labour are surprisingly rare.

In the study published by Vaidya et al (2017),[8] which includes all hospital discharges in pregnant women 18 to 50 years-old from 57,315,593 pregnancy-related hospitalizations between 2000-2012, those authors observed that the overall frequency of any arrhythmia during pregnancy was 68 per 100000, AF 27 per 100 000, atrial flutter 4 per 100000, supraventricular arrhythmia 22 per 100000, ventricular fibrillation 2 per 100000 and VT 16 per 100000 (Figure 1). These data points out an increase of pregnancy-related hospitalizations with arrhythmias by 58% (P<0.001 for trend), from 55 per 100000 in 2000 to 83 per 100000 in 2012, an increase in arrhythmia frequency primarily caused by more AF [(111%; from 18 per 100000 to 35 per 100000; P<0.001 for trend)], and VT [(127% increase; from 10 per 100000 to 21 per 100000; P<0.001 for trend)], whereas SVT remained stable over time [(12% increase; P<0.001 for trend)]. It was also observed an increase in arrhythmia frequency in pregnancy over time being AF the most frequent arrhythmia.

In the last decades, successful treatment of heart disease in children has resulted in an increased prevalence of heart disease in childbearing women,[7,9,10] having their children 5% to 50% probability of cardiac defect compared with 0.8% of all children born in the United States.[7]

Cardiac disease is an important risk factor for maternal cardiac and neonatal complications, being synergic with obstetric risks, with higher miscarriage and caesarean rate.[11,12]

The Vaidya's et al study (2017)[8] also showed that arrhythmias in pregnancy were associated with elevated odds ratio for mortality and greater in-hospital death and maternal or fetal outcomes (Figure 1). Thus a correct identification of the arrhythmia is crucial.[12]

Fortunately, life-threatening rhythm disorders in women of childbearing age are relatively rare, being treatment reserved for haemodynamically unstable arrhythmias or for those causing debilitating symptoms.[12]

Unfortunately, few randomized studies and little data on the efficacy or safety of antiarrhythmic drugs and ablation procedures exist and much of the clinical care is guided by knowledge of pregnancy's physiology and results obtained in general population patients.

Physiological changes during pregnancy

The cardiovascular system suffers significant adaptations during pregnancy, including HR increase about ten beats per minute, an increase of 30-50% in cardiac output (CO) until the 24th week,[13] with the uterus receiving 17% of the CO at term (compared with the usual 2%), an initial decreasing in arterial blood pressure and systemic vascular resistance, reaching its lowest at 20th week[13] (which will gradually increase by mid-pregnancy), where oestrogens, prostaglandins and prolactin have a role.[14] Following this decrease, vascular resistances and secondarily blood pressure begin to rise, approaching the pre-pregnancy values by term.[15] Simultaneously, higher plasma catecholamine concentration and increased adrenergic receptor sensitivity are registered (which can be a result of oestrogens, since they may heighten cardiac excitability as they do in uterine muscle and sensitize the myocardium to catecholamines by increasing the number of alpha-adrenergic receptors),[16] auricular stretch and increased end-diastolic volumes due to intravascular volume expansion, hormonal and emotional changes.[1,2,12,14,15,17] Effectively, normal fetal growth and birthweight are directly correlated with plasma volume expansion degree.[14] The ECG, as already mentioned, can

register decreased PR, QRS and QT intervals, but usually there is no change in P wave, QRS complex or T wave amplitudes.[1,2] It might be possible to find a Q wave and an inverted T wave in the inferior leads.[1] A leftward shift of the electrical axis can occur due to heart rotation secondary to gravid uterus enlargement.[1,2] Pregnancy is unlikely to generate new arrhythmia substrate, but those changes may trigger a pre-existing subtract capable of sustaining an arrhythmia.[1] Main mechanisms of arrhythmia generation during pregnancy are represented on Table 1.

A bigger heart can sustain re-entry more easily and mechanical stretch is known to be arrythmogenic.[1,18]

An increased propensity to ectopic activity is also found[1,2] with a higher resting rate increasing the risk.[19] Also, total body water increase (which can increase from 5 to 8L), blood volume, and capillary hydrostatic pressure increase the volume of distribution of hydrophilic substrates.[12] This can lead to the necessity of higher doses of hydrophilic drugs to obtain therapeutic concentrations.[15,20] Simultaneously, drugs with high protein bound may display higher free levels due to decreased protein binding availability, and thus higher bioactivity,[15,20] despite the low probable clinical impact. The increase in renal blood flow, which can achieve 80% by mid-pregnancy, results in a glomerular filtration rate 50% higher,[5] associated with elevated CO can increase drug clearance.[20] Hepatic metabolism may be increased due to elevated progesterone levels, enhancing clearance of some drugs,[21,22] and gastrointestinal absorption may be altered, due to changes in gastric motility, secretion and pH.[12,20] Phenomena that are necessary to consider by the time of prescription. Pregnancy is also accompanied by changes in haemostasis that produce a hypercoagulable state that helps to prevent possible haemorrhage during delivery or miscarriage,[23] with an increased erythropoiesis.[14] Despite red cell mass raise, plasma volume increases greater and more rapidly, decreasing haemoglobin concentrations, causing physiologic anaemia of pregnancy and hemodilution.[14,15] Most clotting factors increase, while several anticoagulants and fibrinolytic activity decrease.[23,24] This hypercoagulable state may not return to normal ranges for at least eight weeks after delivery.[23]

Figure 2 sums up the main pregnancy's physiological modifications and Figure 3 details the major cardiovascular alterations.

As so, maternal cardiovascular adaptations may unmask previous unknown heart disease and result in significant morbidity and mortality.[14] Although there's an abrupt fall in cardiac demand after delivery, physiological and electrophysiological remodelling of the heart is not instantaneous, turning postpartum heart more similar to the pregnant heart than the pre-pregnancy heart.[3] Most changes are fully reversed in the weeks and months after delivery.[13,14]

Diagnosis

Diagnostic criteria for arrhythmias are not changed by pregnancy.[7] The correct diagnosis of an arrhythmia is of major interest, once a haemodynamically compromising arrhythmia can be a cause of inadequate maternal and placental blood flow,[12] and since it will guide treatment and will define prognosis.[1] By this time, is also important to exclude reversible causes, associated heart disease or systemic disorders such as thyroid dysfunction, since hyperthyroidism occurs in 0.5% of pregnancies,[7] and haemorrhage, pulmonary embolism, infections and inflammatory states in cases of unexplained sinus tachycardia or AF, for example.[1,7] A careful history, including family history, particularly sudden premature or unexplained deaths, and physical examination are needed, associated to an ECG and other diagnostic methods.[1,12] Patient assessment is synthesized on Table 2. By the third trimester, a symptom escalation might be seen and minor arrhythmias may be associated to symptoms as breathless or chest pain.[1]

Palpitations, dizziness, presyncope and even syncope frequently occur during pregnancy, being palpitations the most common symptom.[25] The sensation of palpitations in the absence of concomitant cardiac arrhythmias may be related to physiological changes already mentioned, such as increased HR, decreased peripheral resistance and increased stroke volume.[25]

Maternal and perinatal outcomes

Cardiac maternal disease is a major contributor to maternal and neonatal morbidity, despite low mortality; among these women, those with arrhythmia have an increased risk for cardiac complications in pregnancy.[17,26] In fact, Siu et al (2002)[11] in a study with 302 pregnancies in women with heart disease (structural cardiac lesions or symptomatic cardiac arrhythmias requiring treatment before pregnancy) comparing with a control group of 572 pregnancies without disease, showed that maternal (such as caesarean section, pregnancy-induced hypertension postpartum hemorrhage; cardiac complications such as pulmonary edema, sustained symptomatic tachyarrhythmia or bradyarrhythmia requiring treatment, stroke, cardiac arrest, or cardiac death) and neonatal complications (birth before 37 weeks gestation, small-for-gestational-age birth weight (10^{th} percentile for gestational age), respiratory distress syndrome, intraventricular haemorrhage, fetal or neonatal death and maternal cardiac complications - being heart failure or cardiac arrhythmia the most common cardiac outcomes in 94%) were more frequent in the study group (18% versus 7%). However, only 8% of pregnancies in the heart disease group had arrhythmia (n=23; SVT, VT, or sick sinus syndrome), which was one of the biggest limitations of this study concerning the evaluation of arrhythmias impact on maternal and/or fetal outcomes.[11] Table 3A sums maternal and neonatal outcomes of this study.

Haemodynamic alterations may have consequences on the developing fetus, on antiarrhythmic medications and their teratogenic potential.[17] It is known that New York Heart Association (NYHA) class>II heart failure, cyanosis, smoking, multiple gestation, maternal left heart obstruction and anticoagulants use during pregnancy are predictive of adverse neonatal events.[27] A retrospective study by Henry et al (2016),[17] which included 143 women (n=36 with arrhythmia, 16 of them with structural disease, and n=107 without arrhythmia), tried to determine whether women with cardiac arrhythmia were at increased risk for adverse perinatal outcomes compared with women with other types of cardiac disease but without arrhythmia.[17] Women with arrhythmia (being SVT the most frequent) were more likely to have a spontaneous

vaginal delivery (64% vs 43%), with or without cardiac lesions, and a higher diagnosis rate of intrauterine growth restriction (IUGR) (17% vs 5%) and placental abruption (6% vs 0%).[17] Table 4 summarizes adverse obstetrical and neonatal outcomes by arrhythmia status.

In the same study, other outcomes as fetal demise, preeclampsia, gestational diabetes, chorioamnionitis, postpartum haemorrhage, need for blood transfusion and intensive care unit (ICU) admission weren't significantly different.[17] Despite differences in IUGR diagnosis, a statistically significant difference in neonates' birth weights or in small for gestational age (SGA) rates between the two groups wasn't found.[17] Other study which examined arrhythmias' recurrence rates during pregnancy in women with known cardiac rhythm disorders, such as previous paroxysmal SVT, paroxysmal or persistent AF or atrial flutter and VT, found a recurrence rate of tachyarrhythmia in 44% in women at normal sinus rhythm at baseline, being prematurity the most common adverse fetal event.[28] Another retrospective study showed that women with cardiac disease were more likely to give birth to newborns with low percentile birth weights at an early gestational age.[29] However this was a heterogeneous cohort study which included women with different cardiac disease types and also with different arrhythmias.

Interestingly, data from a recent registry ROPAC (Registry Of Pregnancy and Cardiac disease - ROPAC) reported a 100 times higher maternal mortality rate in women with heart disease compared to the general pregnant population.[30]

In the last decade, more specific data about maternal and fetal outcomes, related to more specific arrhythmias, have been reported in several retrospective studies. Most of them included only small samples, which can preclude robust conclusions about maternal and fetal outcomes.

Despite AF being rare in pregnant women, certain factors such as increased maternal age and white race increase the odds of having AF. However, major maternal and fetal complications are infrequent, albeit a source of concern.[24] Lee et al (2016)[24] described these outcomes (Table 3B).

VT is rare during normal pregnancy (incidence ranging from 1.0% to 1.4% in women with heart disease and 1.6% in women with congenital heart disease; no data in pregnant women with valvular heart disease, ischemic heart disease or cardiomyopathy is reported), but as expected, it could promote maternal haemodynamic compromise causing safety concerns and serious consequences to both mother and fetus.[31]

Ertekin et al (2016)[31] published a retrospective study, which included 2966 pregnancies in women with structural heart disease. Forty-two women (1.4%) developed clinically relevant VT during pregnancy, more frequently in the third trimester (48%), being NYHA class>1 before pregnancy an independent predictor. Outcomes are described on Table 3C.

General Treatment

Several arrhythmias in pregnant women can provoke haemodynamic compromise, namely low blood pressure and low tissue perfusion levels. The uterus receives 17% of the CO at term (compared with the usual 2%). If the mother's perfusion is compromised, uterine vasoconstriction is provoked to allow vital maternal organ perfusion.[7] At the end of pregnancy, the uterus can obstruct the venous return through the inferior vena cava, which can lead to the necessity of lying the pregnant women on her left side during a symptomatic arrhythmia.[7] Thus, pregnancy adds urgency to treatment.

The decision of treating depends on arrhythmias' frequency, duration and tolerability, always balancing pros and cons of not treating compared with antiarrhythmic drugs' side effects for both mother and fetus.[1,2] The major risk to the fetus is during organogenesis which is completed by the end of first trimester.[1,20,24] By the second and third trimesters, medication may have potential effects on fetal growth or lead to fetal arrhythmias.[24] No antiarrhythmic drug is entirely safe during pregnancy, so drug therapy must be avoided during the first trimester if possible and drugs with the longest record of safety should be used as the first line therapy.[2]

Most commonly used antiarrhythmic drugs cross the placental barrier in some extent, resulting in fetal exposure and most are categorized as Food and Drug Administration (FDA) class C:

“animal reproduction studies have been shown to have an adverse effect of the fetus and there are no controlled studies in women or there are no animal or human studies. Drugs should be used only if the potential benefits justify the potential risks to the fetus”.[7,20,32] FDA categories are exposed on Table 5.

There are fundamental principles when managing arrhythmias during pregnancy. It’s essential to correctly diagnose the arrhythmia, the necessity for treatment must be evident, the number of drugs used and their doses must be the lowest, and the chosen drug must have a history of safe use in pregnant women.[12]

Arrhythmias’ treatment during pregnancy is in general similar to that of the non-pregnant women.[2,19] Usually there’s no need for drug therapy for the management of supraventricular or ventricular premature beats, but stimulants such as tobacco, caffeine and alcohol must be avoided.[2]

Asymptomatic arrhythmias shall not be treated unless they are life threatening.[1]

Table 6 summarizes the main antiarrhythmic drugs characteristics and safety profile during pregnancy and breastfeeding.

Electrical cardioversion is necessary in all patients who are haemodynamically unstable (hypotensive, had a syncope, or with angor or clinical heart failure).[2]

Specific clinical situations and arrhythmias

The most common arrhythmias during pregnancy seem to be sinus tachycardia, sinus bradycardia or sinus arrhythmia (104 episodes/100000 pregnancies), followed by paroxysmal SVT, which is more frequent during third trimester or peripartum, and premature beats (24/100000 pregnancies),[4] although AF was the most prevalent in the ROCAD registry (27 per 100000).[8]

Both premature extra beats and sustained tachyarrhythmias become more frequent and may even manifest for the first time during pregnancy.[33] The 25% increase in HR explains how sinus tachycardia is not uncommon during pregnancy, especially in the third trimester.[1] In fact, sinus tachycardia is common in young women but doesn't adversely affect pregnancy, being a normal response to pregnancy,[5] and unless associated with unacceptable symptoms, treatment of sinus tachycardia is unacceptable.[7]

Most recorded arrhythmias are of supraventricular origin.[9] Ectopic beats and non-sustained arrhythmia are encountered in more than 50% of pregnant women investigated for palpitations while sustained tachycardias are less common.[1] Pathological bradycardia is rare, being often diagnosed before the patient reaches childbearing age, and is usually well tolerated, and frequently secondary to congenital heart block.[1,2,12]

Arrhythmias in patients without underlying structural heart disease are likely to be pathway-related SVT, such as atrioventricular nodal re-entry, or idiopathic VT.[10,18] By contrast, in patients who have cardiomyopathy, rheumatic, or other valve disease, or who have undergone corrective cardiac surgery for congenital heart disease, the mechanism is likely to be atrial or ventricular tachyarrhythmia related to the pathological substrate.[2,10]

During labour and delivery ECG resting abnormalities were found in the majority of pregnant women, including premature atrial, ventricular or nodal complexes, sinoatrial arrest, wandering atrial pacemaker, sinus tachycardia and paroxysmal VT.[2]

In the Table 7 are expressed "more" specific arrhythmia treatment.

Bradycardia

Pathological bradycardia is rare, since usually bradyarrhythmias are well tolerated,[1,2] and frequently diagnosed before childbearing age.[12]

Some women with physiological bradycardia may become more symptomatic by the second trimester as their blood pressure drops due to systemic resistance reduction.[1] Treatment is

rarely required.[1] In rare cases, sinus bradycardia has been attributed to the supine hypotensive syndrome of pregnancy, with uterine compression of inferior vena caval blood return causing paradoxical sinus slowing, which responds to maternal change of position (left lateral decubitus).[1,33,34] It can also appear as a reflex cardiac slowing during delivery (Valsalva manoeuvre).[33] The use of a temporary pacing for delivery is discussed, since the Valsalva manoeuvre associated with delivery increases the chance of worsening bradycardia and syncope, and pacing would allow an adequate HR response to increased cardiovascular stress. However, experience shows that the inserted device is rarely used, and probably women with complete AV block, which is rare in pregnant women, (congenital 3rd degree AV block; narrow QRS complex) who do not require a permanent pacemaker, can be managed in labour without temporary pacing.[35] Spinal anaesthesia for caesarean section, however, can be associated to all bradycardia grades higher incidence, especially with high spinal blocks, although most of the registered arrhythmias were transient and recovered spontaneously.[36] The use of atropine in pregnancy is extremely limited, but does not currently indicate an increased risk of fetal malformation.[37]

Hidaka et al (2011)[38] recently outlined that most women with complete AV block who are asymptomatic and do not require a permanent pacemaker before delivery, can be safely managed during labor without pacing. A pacemaker is indicated in the presence of symptoms (chest pain, dyspnea, syncope, palpitations), QT interval prolongation, wide QRS complex, ventricular dysfunction, or heart failure. Permanent pacemakers are implanted, using echocardiographic guidance,[2] at any stage of pregnancy whereas short-term temporary pacing is done during delivery.

Supraventricular tachycardia (atrioventricular nodal re-entrant tachycardia and atrioventricular re-entry tachycardia)

Paroxysmal SVT is the most common non-sinus tachycardia in women of childbearing age.[7] Narrow QRS complex tachycardia usually presents with palpitations, shortness of breath or anxiety.[34]

First onset of paroxysmal SVT during pregnancy seems rare,[39] but previously diagnosed SVT may increase in frequency or severity.[12,39] Independently of the mechanism of the SVT, vagal stimulation manoeuvres should be the first choice once they may terminate the episode.[2] When these manoeuvres fail, rapid intravenous bolus adenosine can be used, with escalating boluses up to 18-24 mg until the desired response is achieved, since it will depress AV nodal conduction and sinus node automaticity.[1,5] Adenosine efficacy in terminating paroxysmal SVT is very good (approximately 84% to 90% of maternal cases), and normal sinus rhythm is restored after one to two minutes; increasing dose to 15 mg in one study led to fetal bradycardia in one patient, which reverted back to normal within 10 minutes of administering bolus. Adenosine use in first trimester is still not advised due to lack of sufficient studies, but during second and third trimesters, its administration is safe.The enzyme responsible for adenosine degradation, adenosine deaminase, decreases by about 25%[21] and therefore most women respond to lower doses (between 6-12 mg).[1] As it doesn't cross the placenta, possibly because of the short elimination time, which is estimated to be 10 seconds,[40] it has no effect on the monitored fetal HR.[10,12] Verapamil is an effective second line treatment; treatment with propranolol or metoprolol would also be appropriate.[1,7,12,34] Verapamil can be used in doses up to 10 mg without affecting fetal HR. However, fetal distress has been associated with verapamil induced maternal hypotension, bradycardia, heart block and fetal demise. Beta-blockers are the drugs of choice in women with known Wolf-Parkinson-White (WPW), as AV nodal blocking drugs such as digoxin and calcium channel blocking drugs may accelerate conduction through the accessory pathway and deteriorate maternal condition.[1]

Prophylactic antiarrhythmic drug therapy should be used only if symptoms are intolerable or if the tachycardia causes haemodynamic compromise.[33] Any haemodynamically unstable SVT that may be compromising blood flow to the fetus should be electrically cardioverted,[12,34] although its high recurrence rates.[41] In Table 8 European Society of Cardiology (ESC) recommendations are presented.

Atrial Fibrillation/Atrial Flutter

AF and atrial flutter are rare during pregnancy and seem secondary to congenital or valvular heart disease, hypertrophic cardiomyopathy, or underlying metabolic disturbances such as thyrotoxicosis and electrolyte perturbations.[1,2,12,23] However it can represent a benign episode of lone AF in a pregnant woman with a normal heart.[23] A rapid ventricular response to these arrhythmias can lead to haemodynamic compromise and result in increased risk to mother and fetus.[24,33] Increased cardiac demand during pregnancy can make AF less tolerated and increase the risk of heart failure.[24] The odds of having clinically significant AF episodes is significantly increased during third trimester (Table 9) compared to first trimester, probably related to plasmatic volume expansion, red cell mass increase that peaks at 28 to 34 weeks of gestation, and cardiac load increase.[24] Delivery haemodynamic changes appear important, since many cases during third trimester occurred within 24 hours of delivery.[24] Postpartum the risk declines to baseline levels.[24]

Due to hypercoagulable state and potential detrimental effects of fast ventricular rates on the fetus, it's important to treat early.[2] The goal will be the conversion to sinus rhythm, being ibutilide or flecainide effective, or ventricular rate control by a cardioselective beta-adrenergic blocker drug alone (drug of choice) or in combination with digoxin; verapamil and diltiazem are also effective.[2,33] In fact, ibutilide or flecainide are usually effective in AF and atrial flutter pharmacological termination in haemodynamically stable patients with structurally normal heart, and are useful when deep sedation needed for electrical cardioversion is undesirable due to unpredictable haemodynamic response, for example.[33,42] Intravenous agent ibutilide has 1.7% possibility of inducing *torsades de pointes* (25 mcg to 1 mg dose of IV ibutilide can be administered over 10 minutes; this can be repeated after 30 minutes if conversion to normal sinus rhythm is not achieved). Amiodarone should only be used in emergent situations when all other agents and techniques have failed.[43]

Cardioversion management can be found on Figure 4. Electrical cardioversion should be performed in pregnant patients who are haemodynamic unstable[33] [consider electric cardioversion (50–100 J for AF and 25–50 J for atrial flutter)].

For HR control of AF, β-blockers are recommended as first choice.[33]

Ventricular tachycardia

VT is rare in healthy women without underlying organic heart disease. Physical and psychological stress are stimuli for its precipitation in a majority of pregnant women without structural heart disease.[2] VT may cause hypotension and even collapse if the rates are high enough, severely compromising both maternal and fetal circulation.[10] Particularly polymorphic VT has a high risk of degenerating into ventricular fibrillation.[1]

The clinical risk of nonsustained ventricular arrhythmias in patients with structurally normal hearts is low.[5,12] VT in pregnant woman may be due to peripartum cardiomyopathy, arrhythmogenic right ventricular dysplasia, congenital long QT syndrome (LQTS), hypertrophic cardiomyopathy and rarely coronary artery disease.[12] If haemodynamically unstable, it must undergo emergent electrical cardioversion.[12] If stable, lidocaine may be given, having few adverse fetal effects, although crossing the placental barrier.[12] Other options are sotalol, procainamide or amiodarone, which should only be used if VT persists.[33,41] The most frequent type is idiopathic right ventricular outflow tract tachycardia, which should be treated with verapamil or a beta-blocker if associated with severe symptoms (or haemodynamic compromise – electrical cardioversion with 50 to 100J, if the first shock is ineffective, increase energy to 100 to 360J); catheter ablation must be considered when all other therapies have failed. [33,43] Sustained or recurrent VT may require chronic antiarrhythmic therapy,[12] being most of them idiopathic.[5] These cases are associated to normal hearts with idiopathic catecholamine-sensitive VT, being cardioselective beta-blockers the therapy of choice, such as metoprolol and propranolol.[5,12,43] Propafenone and flecainide have shown to be relatively safe and effective for structural heart disease patients' prophylactic therapy.[43] Amiodarone

and/or implantable cardioverter-defibrillator (ICD) should be considered to treat therapy-resistant VT.[33] Peripartum cardiomyopathy should always be considered with new-onset VT within 6 months of delivery.[2,5] Table 8 ESC recommendations.

Implantable cardioverter-defibrillators

The main reasons for ICD implantation in young women are structural heart diseases, such as dilated cardiomyopathy, hypertrophic cardiomyopathy and inherited arrythmogenic diseases, such as LQTS.[44] As more of these women achieve childbearing age, the number of ICD devices has increased dramatically.[45]

Patients who present with unstable ventricular arrhythmias and at high risk for sudden cardiac death during pregnancy may be candidates for ICD implantation.[32]

In the past, women with ICD were advised not to get pregnant, since the possible effects of ICD on pregnancy were unknown.[46]

Nowadays, having an ICD should not defer a woman from becoming pregnant, unless contraindicated by structural cardiac disease.[46] Pregnancy doesn't seem to increase the risk of major ICD-related complications or result in a high number of ICD discharges.[46] According to Boulé et al (2014),[45] pregnancy has no effect on ICD operation and there's no link between carrying an ICD and adverse pregnancy outcomes, although the same authors, in a study of 20 pregnancies with pre-pectoral ICDs with bipolar transvenous endocardial leads, described a pregnant woman who was subjected to two ICD shocks at 4 weeks gestation and miscarried her pregnancy seven days later; the authors consider that this can be accounted for typical rates of idiopathic miscarriage or this can be a result of the ICD shocks, and referred that no other study has ever been associated with an adverse fetal outcome, but they also refer that no other cases of ICD shocks delivered during pregnancy reported on literature were at such early stage of pregnancy, suggesting that the timing of ICD shock might be a determinant of fetal outcome.[45] On the same study no device-related complications were reported.[45]

In a study of 44 pregnant women with ICD (42 located in the abdomen, 2 implanted in the prepectoral position, 30 with epicardial and 14 with transvenous lead systems), the incidence of caesarean section, spontaneous abortion, preterm delivery and fetal growth retardation were similar to that expected in the general population.[46] In the same study, 82% of pregnant women with ICDs experienced no complications. However, the remaining pregnant women (18%) had a medical or device-related complication, such as tenderness at the ICD pocket scar, generator migration, pericarditis secondary to the epicardial patches, pulmonary embolism, therapeutic abortion, worsening hyperthyroidism, congestive heart failure and weight loss.[46] Labour associated contractions are intense enough to affect the muscles located in the upper torso and shoulder and therefore could apply stress to the transvenous system, however, no lead fractures were reported, not even in patients with transvenous system.[46] No complications related to the device were reported, such as lead dislodgement, lead dysfunction or lead thrombus.[45,46] The hormonal and autonomic alterations and the strong uterine contractions during delivery didn't precipitate any arrhythmias or ICD firings. The ICD on/off status during delivery appears to be irrelevant on the overall outcome.[46] The authors recommend leaving the device "on" (full therapy mode) during vaginal deliveries, since if any arrhythmia develops more prompt therapeutic intervention can be delivered than that by external defibrillation, in the cases of Caesarean-section the device must be "off" (monitor only) because cautery is involved.[46,47]

Other retrospective study published by Schuler et al (2012)[47] concluded that pregnancy outcome overall is good, but medical and/or device complications are frequent. They reported in 19 pregnancies one thrombotic event with the development of a thrombus on a ventricular lead in a patient with previously undiagnosed thrombophilia, arrhythmia episodes were not uncommon, and it was registered one lead fracture. Therefore these patients must be considered a high-risk pregnancy group who require specialist multidisciplinary team antenatal care.[47]

Table 10A summarizes the results from different studies.

It is unlikely that ICD firings cause life-threatening fetal arrhythmias, since fetal heart has high fibrillation threshold and the amount of current reaching the uterus must be small once therapy from internal defibrillation is very directed.[46] This theory was defended for many years, but Barnes et al (2002)[48] reported a tightly contracted uterus and fetal bradycardia after a low energy (50J) transthoracic shock, which was hypothesised to be due to the shock. Other works suggest that uterine muscle and amnion fluid are excellent electric conductors, and, although the uterus is usually not involved in the electric cardioversion trajectory and only a minimum amount of current reaches the uterus, the placement of the pads over the apex beneath the left breast or the relatively large third trimester uterus can influence the result of the shock.[48-50] These can challenge the past belief and suggest that undesirable effects can result from ICD shock therapy in very early stages of pregnancy.[45] If this is verified, the strict compliance to Beta-blocker therapy becomes even more important throughout pregnancy for women carrying ICDs.[45] In fact, as heart rates may increase during labour and delivery, an inappropriate shock might be delivered, being antiarrhythmic agents important on this control.[44]

Although direct current exposure to the fetus is minimum, fetal monitoring during the procedure is recommended.[10] In later stages of pregnancy there is a theoretical risk of initiating preterm labour.[32]

In Table 10B are presented possible problems with ICD therapy during pregnancy.

When indicated, a single-chamber device is preferred and is usually well tolerated after the eighth week of gestation. Echocardiography guidance should be used to avoid fetal radiation exposure during implantation.[10,33] There are no fixed ICD parameters during pregnancy. Programming and follow-up should be highly individualized and supervised by experienced cardiac electrophysiologists.[10]

Thus, clinical stable women who desire to have a child shouldn't be routinely discouraged from getting pregnant based on ICD presence, at the same time the number of women with an ICD reaching childbearing age and desiring to get pregnant will continue to increase.[45,46,51]

Catheter ablation

Catheter ablation may be necessary in poorly tolerated tachycardias and should only be undertaken when reasonable medical therapy is ineffective and the potential risks to the mother and the fetus are outweighed by the expected benefit.[32,33] The risks include fetal radiation exposure and fetal compromise in the event of maternal haemodynamic instability. Also the gravid uterus may difficult patient positioning.[32] Due to the high radiation exposure, ablation should be postponed to the second trimester.[33] Abdominal shielding should be routinely used in pregnancy.[32]

Conclusion

Despite being common, the majority of cardiac arrhythmias is benign. Their management, when needed (since some may have impact on maternal and neonatal outcomes), might be a challenge, mainly because existing data is based on retrospective studies and small samples, being information scarce adding drugs' potential teratogenicity. In fact, prospective studies are needed.

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List of Figures

List of Tables

Figures

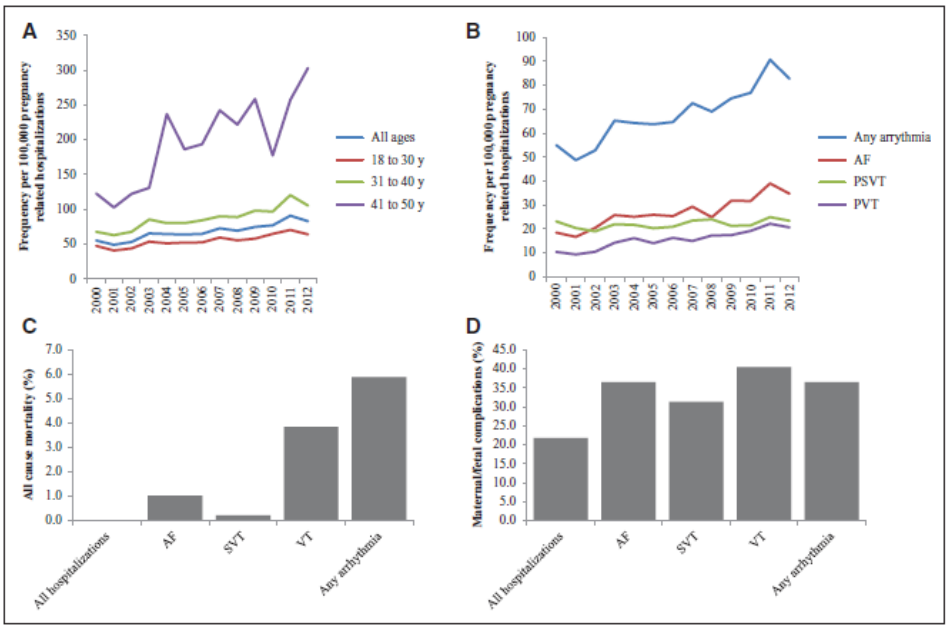


Figure 1 Frequency of arrhythmia in pregnancy and associated mortality and complications.

A - Frequency of any arrhythmia per 100000 pregnancy-related hospitalizations for the entire study period, stratified by age. Greater in pregnant women 41 to 50 years of age (199 per 100 000 and 162% increase) compared with women 18 to 30 years of age (55 per 100 000 and 58% increase).

B - Frequency of arrhythmias per 100000 pregnancy-related hospitalizations by arrhythmia type for the entire study period (see text).

C - All-cause mortality in percentage for the entire study period. With elevated odds ratio for mortality (AF: odds ratio 13.1, 95% CI 7.77–22.21, *P*<0.0001; SVT: odds ratio 6.32, 95% CI 2.41–16.61, *P*<0.001; VT: odds ratio 40.89, 95% CI 26.08–64.1, *P*<0.0001).

D - Maternal/fetal complications (including preterm labour, ante- or postpartum hemorrhage, preeclampsia, eclampsia, gestational hypertension, transfusion, postpartum infection, and fluid and electrolyte imbalance) in percentage for the entire study period. Pregnancy-related hospitalizations with any arrhythmia had overall greater frequencies of in-hospital death (5.9%) and maternal or fetal complications (36.5%) compared with all women (0% and 21.8%, respectively).

AF: atrial fibrillation; SVT: supraventricular tachycardia; VT: ventricular tachycardia.

Taken from Vaidya at al (2017).[8] (with permission from authors).

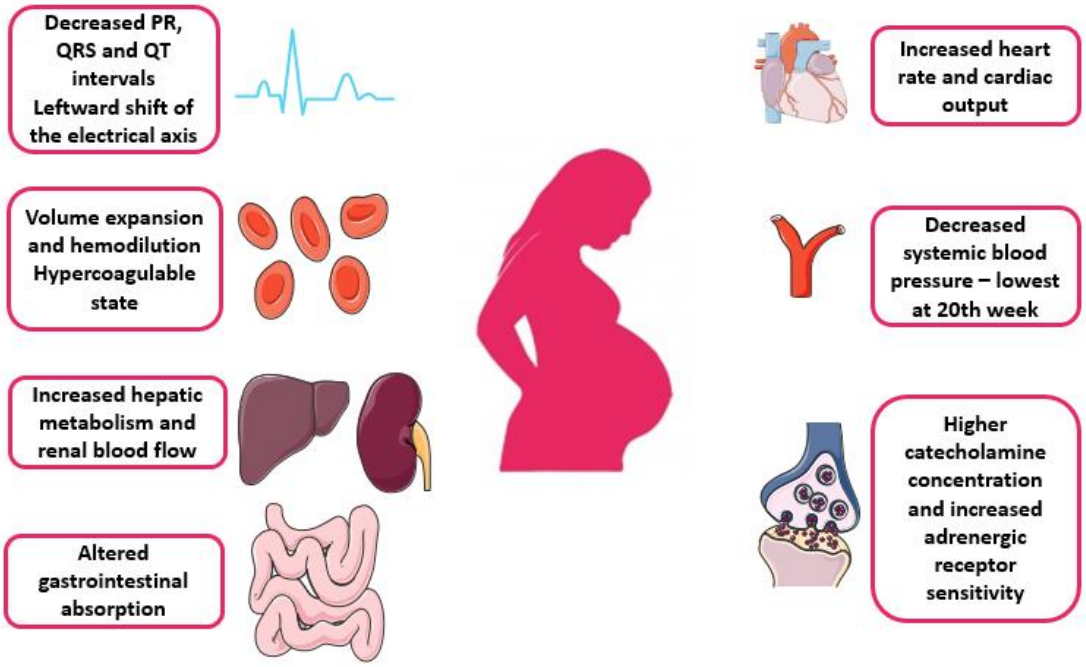
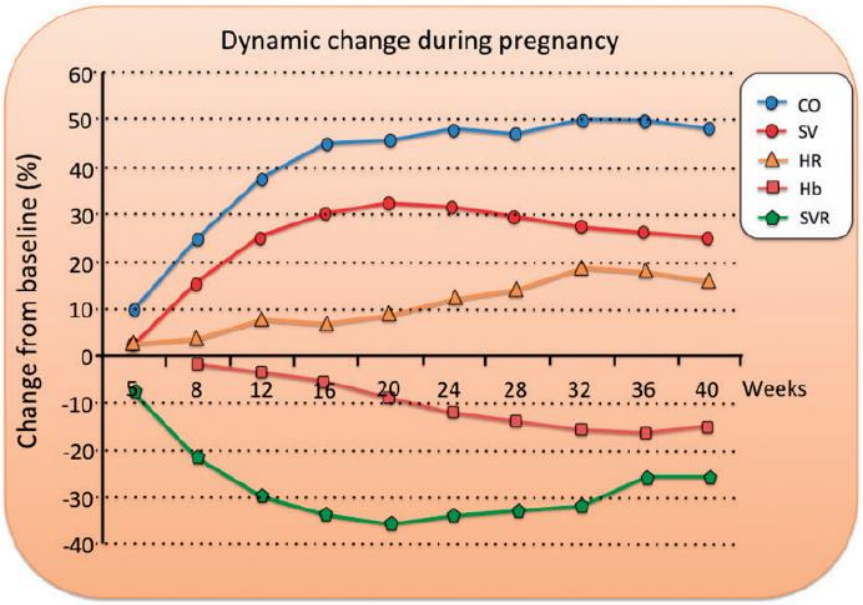


Figure 2 Summary of physiological changes in pregnancy.

A – Cardiovascular dynamic changes during pregnancy.[52]



B – Key cardiovascular physiological changes which occur during pregnancy (another perspective).[53]

Variable	First trimester	Second trimester	Third trimester	Early post-partum
SVR	↓	↓	↓–with a late rise	↑
Heart rate	↑	↑	↑	↓
LVEDD	↑	↑	↑	↓
LV mass	↑	↑	↑–with a late drop	↓
Cardiac output	↑	↑	↑–with a late drop	↓
LV longitudinal strain	No change	No change	↓	↑

Figure 3 Cardiovascular dynamic/physiological changes during pregnancy.

A – Cardiovascular dynamic changes during pregnancy

During pregnancy an increase of CO (which can peak a 50% change from the baseline), SV and HR is expected. Hb and SVR decrease, the last one reaching its lowest value by 20th week, decreasing almost 40% from the baseline value.

CO: cardiac output; Hb: haemoglobin: HR: heart rate; SV: systolic volume; SVR: systemic vascular resistance.

Taken from Bianca et al (2017).[52] (with permission from authors).

B – Key cardiovascular physiological changes which occur during pregnancy (another perspective)

During the three trimesters SVR drops (with a late rise on the third trimester), while heart rate, LVEDD; LV mass and cardiac output increase. LV longitudinal strain decreases only on third trimester. All appear to be reversible early post-partum.

LV: left ventricular; LVEDD: LV end diastolic diameter; SVR: systemic vascular resistance.

Taken from Ashrafi, Curtis (2017).[53] (with permission from authors).

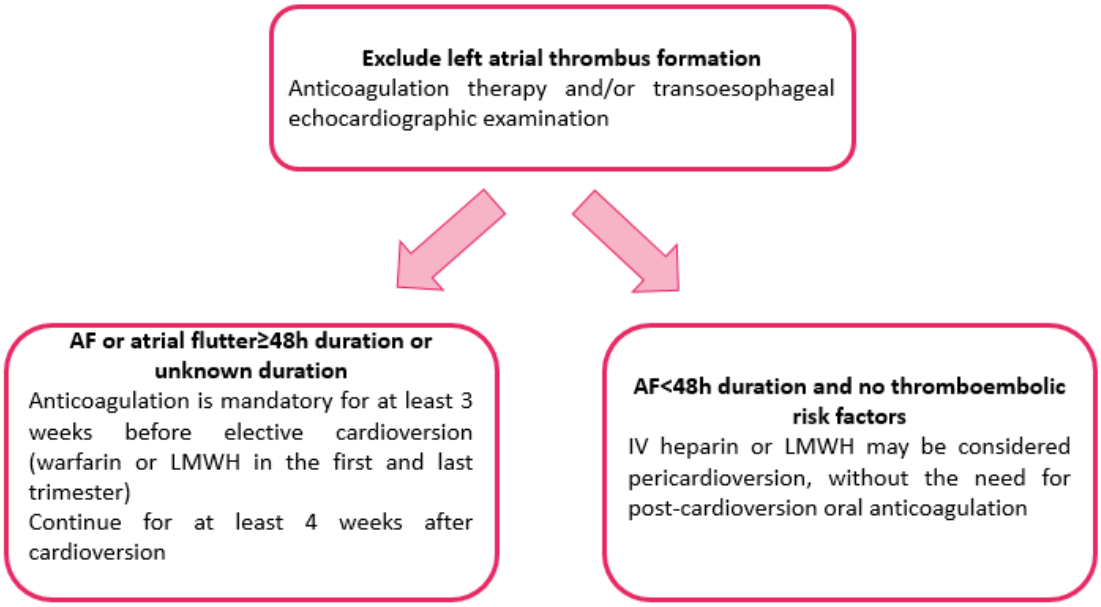


Figure 4 Atrial fibrillation and atrial flutter cardioversion management.[33]

AF: atrial fibrillation; LMWH: low molecular weight heparin.

Tables

Table 1. Main mechanisms of arrhythmia generation during pregnancy.[1]

Structural Heart Disease	**Congenital heart disease creating re-entrant circuits**	1.Acyanotic heart disease, eg: ASD/VSD 2.Cyanotic heart disease, eg: tetralogy of Fallot 3.Valvular heart disease, eg: bicuspid aortic valve
	Acquired	1.Valvular heart disease secondary to rheumatic fever 2.Valvular heart disease secondary to endocarditis 3.Cardiomyopathy
Structural Normal Heart	**Congenital "electrical only" disease**	1.Dual AV nodal pathways causing AVNRT 2.WPW/accessory pathway 3."Channelopathy"
	Acquired	1.Degenerative disease of conduction system 2.Acquired long QT syndrome, eg: drugs, metabolic

ASD: atrial septal defect; AV: atrioventricular; AVNRT: atrioventricular nodal re-entrant tachycardia; VSD: ventricular sepal defect; WPW: Wolf-Parkinson-White syndrome.
Taken and adapted from Adamson and Nelson-Piercy (2017).[1]

Table 2. Patient assessment – Diagnosis.[1,12]

History	Timing, length, degree of symptoms, aggravating and alleviating factors, haemodynamic instability (dizziness, syncope and near syncope), exclude other causes such as thyrotoxicosis
Physical examination	Similar to that in a non-pregnant woman. Findings considered normal: soft systolic flow murmur (increased flow across pulmonary artery and valve), split of the first heart sound and expiratory splitting of the second heart sound in late pregnancy, mild peripheral oedema. Abnormal: mitral stenosis murmur, signs of congestive heart failure, murmurs consistent with congenital heart disease
ECG	Leftward shift in the QRS axis, decreased PR, QRS and QT intervals, but usually there is no change in P wave, QRS complex or T wave amplitudes
Echocardiography	Diagnose structural or functional heart disease, exclude left ventricular dysfunction; transthoracic echocardiogram can be useful to identify congenital or acquired heart disease
Tilt-table testing	Rare in pregnancy, for pregnant patients with undiagnosed syncope. Usually it can be delayed until after pregnancy. Difficult beyond 24 weeks since women are unable to lie flat on their backs as the gravid uterus impedes inferior vena cava flow
Exercise treadmill testing	Rare, to evaluate exercise-induced symptoms, ischemia as a substrate for an arrhythmia and suspected chronotropic incompetence
Ambulatory monitoring	Holter monitor, event monitor, continuous loop monitor (if less frequent symptoms). If no arrhythmia is documented, the patient is unlikely to have a life-threatening arrhythmia
Cardiac catheterization	Rare
Electrophysiological study	Should be avoided since fluoroscopic guidance is used for catheter positioning. The risk of radiation exposure is bigger during the first 51 days of organogenesis. Radiation exposure is associated to congenital malformations, mental retardation and increased risk of childhood malignancies. Catheter placement guided by echocardiography has been described. Rarely necessary since the arrhythmia can usually be managed pharmacologically until after delivery

ECG: electrocardiogram.

Taken and adapted from Adamson, Nelson-Piercy (2007)[1] and Kron, Conti (2007).[12]

Table 3. Pregnancy arrhythmias, cardiac events and outcomes.
A - Outcomes of completed pregnancies.[11]

	Heart disease N=302* N(%)	Controls N=572 N(%)
Caesarean section	**88 (29)**	**129 (23)**
Any neonatal event	**54 (18)**	**40 (7)**
Birth at <37 weeks' gestation	**46 (15)**	**29 (5)**
Birth weight <10th percentile for gestational age	11 (4)	9 (2)
Respiratory distress syndrome	**7 (2)**	**1 (0.2)**
Intraventricular haemorrhage	1 (0.3)	0
Fetal or neonatal death	**10 (3)**	**4 (0.7)**
Birth at <37 weeks' gestation from premature onset labour	**31 (10)**	**23 (4)**
Pregnancy-induced hypertension	16 (5)	21 (4)
Postpartum haemorrhage	8 (3)	9 (2)
Maternal cardiac complications+	**52 (17)**	**0**
Noncardiac death	1 (0.3)	0

B - Maternal cardiac events and obstetric outcomes.[24]

	Number of cases (% Total) (N=157)
Maternal cardiac events other than arrhythmia	
Heart failure/pulmonary oedema	2 (1.2)
Stroke/systemic emboli	0
Cardiac death	0
Obstetric complications	
Any	34 (21.7)
PHTN	17 (10.8)
Preeclampsia	6 (3.8)
Eclampsia	0
PROM	5 (3.2)
Premature labour (<37 weeks of gestation)	9 (5.7)
Postpartum haemorrhage	5 (3.2)
Placental abruption	1 (0.6)

C - Pregnancy outcomes in cardiac patients with and without VT.[31]

	Patients with VT (n=42)	Patients without VT (n=2924)	p-Value
Maternal mortality (%)	2.4	0.3	0.15
Heart failure (%)	24	12	**0.03**
Thromboembolic events (%)	0	0.8	1.00
Endocarditis (%)	0	0.2	1.00
Bleeding during pregnancy (%)	4.8	6	1.00
Intra-uterine growth retardation (%)	4.8	4.6	0.72
Pregnancy induced hypertension (%)	0	2.4	0.63
(Pre)eclampsia (%)	0	2.5	0.63
Caesarean section (%)	68	47	**0.01**
Miscarriage (<24 weeks; %)	0	2.7	0.26
Late fetal death (≥24 weeks; %)	0	0.7	1.00
Neonatal death (%)	4.8	0.3	**0.01**
Median pregnancy duration (weeks)	37.4	39.0	**<0.001**
Apgar score <7 (%)	25	7.3	**0.001**
Preterm birth (<3 weeks; %)	36	16	**0.001**
Low birthweight (<2500g; %)	33	15	**0.001**
Median birthweight (g)	2730	3020	**0.006**
Corrected mean birthweight[+] (g)	3283	3289	0.94

A - *Arrhythmias only accounted for 23 of the total events on the heart disease group.
[+]Cardiac death, stroke, pulmonary oedema, tachyarrhythmia, or bradyarrhythmias. Being heart failure or cardiac arrhythmia the most common cardiac outcome (94%).
Significant correlations are in bold.
Taken and adapted from Siu et al (2002).[11]

B - PHTN: pregnancy-induced hypertension; PROM: premature rupture of membranes.
Taken and adapted from Lee et al (2016).[24]

C - *P-value represents t-test for comparisons of means or Chi-2 test for comparisons of proportion.
[+]Birthweight corrected for: gestational age, fetal sex, maternal age and diabetes.
Significant correlations are in bold.
Heart failure was more common in women with VT, these women also delivered more frequently by caesarean section. Neonatal death, preterm birth, low birthweight and Apgar score <7 occurred more frequently in women with VT. As other studies, one of its limitations is the small sample.
VT: ventricular tachycardia.
Taken and adapted from Ertekin et al (2016).[31]

Table 4. Adverse obstetrical and neonatal outcomes by arrhythmia status.[17]
A – Adverse obstetrical outcomes by arrhythmia status

	Arrhythmia N=36 N (% or ± SD)	No Arrhythmia N=107 N (% or ± SD)	P-value*
Gestational age at delivery (weeks)	37.9 (±2.2)	37.3 (±3.3)	0.48
IUFD	0 (0)	2 (2)	0.41
Preeclampsia	2 (6)	10 (9)	0.48
IUGR	6 (17)	5 (5)	**0.02**
GDM	2 (6)	8 (7)	0.70
Blood transfusion	1 (3)	13 /12)	0.10
Chorioamnionitis	0 (0)	8 (7)	0.09
Abruption	2 (6)	0 (0)	**0.01**
Postpartum haemorrhage	6 (17)	29 (27)	0.21
ICU admission	2 (6)	18 (17)	0.09

B – Neonatal outcomes by arrhythmia status

	Arrhythmia N=36 N (% or ± SD)	No Arrhythmia N=107 N (% or ± SD)	P-value*
Gestational age at delivery (weeks)	37.9 (±2.2)	37.3 (±3.3)	0.48
Preterm delivery	7 (19)	25 (23)	0.63
Birth weight (gms)	3019 (±661)	2873 (±773)	0.15
SGA	2 (6)	12 (11)	0.33
5 min APGAR < 7	6 (17)	12 (11)	0.39
NICU admission	10 (28)	33 (31)	0.73

GDM: gestational diabetes mellitus; ICU: intensive care unit; IUFD: intrauterine fetal demise; IUGR: intrauterine growth restriction; NICU: neonatal intensive care unit; SGA: small for gestational age, less than 10%.
***P-value represents t-test for comparisons of means or Chi-2 test for comparisons of proportion.**
Significant correlations are in bold.
Taken and adapted from Henry et al (2016).[17]

Table 5. US Food and Drug Administration classification for drugs used during pregnancy.[32]

FDA Category	Definition
A Controlled studies show no risk	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). The possibility of fetal harm seems remote.
B No evidence of risk in studies	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; or animal studies have shown an adverse effect that was not confirmed in controlled studies in pregnant women. The possibility of harm seems remote but cannot be ruled out.
C Risk cannot be ruled out	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in women or there are no animal or human studies, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D Positive evidence of risk	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in women. The potential benefits of the drug may outweigh the potential risks, but the patient should be apprised of the potential risk to the fetus.
X Contraindicated in pregnancy	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, or both, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. The drug is contraindicated in women who are pregnant or may become pregnant.

Taken and adapted from Enriquez et al (2014).[32]

Table 6. Characteristics and safety of antiarrhythmic drugs during pregnancy and breastfeeding.[12,21,32,41,54-56]

Use during Pregnancy				Use during Breastfeeding	
Drug (Vaughan–Williams Class)	FDA risk category	Safety profile (Potential adverse effects/ Reported Negative Fetal Effects)	Teratogenic	Compatibility	Reported Negative Neonatal Effects
Class I (Sodium channels blockers)					
IA					
Quinidine	C	Neonatal thrombocytopenia, VII nerve toxicity, premature birth, *torsades de pointes*	No	Compatible	None
Procainamide	C	Lupus-like syndrome, *torsades de pointes*, agranulocytosis	No	Compatible (for short term use)	None
Disopyramide	C	Uterine contractions	No	Compatible	None
IB					
Lidocaine	B	Bradycardia, CNS toxicity, acidosis	No	Compatible	None
IC					
Flecainide	C	Well tolerated	No	Compatible	Not described
Propafenone	C	Well tolerated	No	Unknown	-
Class II (Beta blockers)					
Metoprolol	C	Bradycardia, hypoglycemia, growth retardation, apnea	No	Compatible	None
Bisoprolol	C	Bradycardia and hypoglycemia in fetus	No	-	-
Atenolol	D	Hypospadias (first trimester), birth defects, low birth weight, growth retardation, bradycardia and hypoglycemia in fetus (second and third trimester)	No	No	Cyanosis, bradycardia
Propranolol	C	Bradycardia, hypoglycemia, growth retardation, apnea	No	Compatible	None
Class III (Potassium channels blockers)					
Amiodarone	D	Fetal hypothyroidism, goiter, growth retardation, bradycardia, premature birth, prolonged QT interval, spontaneous abortion	Yes	Avoid	Possible hypothyroidism
Sotalol (beta-blocker also)	B	*Torsades* de pointes, transient fetal bradycardia, hypoglycemia	No	Compatible	Not described
Ibutilide	C	*Torsades* de pointes	Unknown	Unknown	-

Class IV (Calcium antagonists)					
Verapamil	C	Fetal bradycardia, heart block, maternal hypotension (with IV administration)	No	Compatible	None
Diltiazem	C	Possible teratogenic effects similar to verapamil	Unknown	Compatible	None
Others					
Adenosine	C	Dyspnea, bradycardia	No	Unknown	-
Digoxin	C	Low birth weight	No	Compatible	None
Magnesium sulphate	D	Neuromuscular and/or respiratory depression in newborn (if administered in hours before the labour), skeletal abnormalities (if administered continuously for >7 days)	Yes	Compatible	None

-: insufficient data; CNS: central nervous system; FDA: Food and drug administration.

Taken and adapted from Kron and Conti (2007),[12] Joglar and Page (1999),[21] Enriquez et al (2014),[32] Yaksh et al (2016),[41] Joglar and Page (2014),[56] Ersboll et al (2014)[55] and Widerhorn et al (1991).[54]

Table 7. Treatment of specific arrhythmias.

Arrhythmia	Characteristics	Treatment
Bradycardia	Rare. Sometimes due to inferior vena cava uterine compression. Valsalva manoeuvre during delivery may worsen.	Rarely required. Maternal change of position. Atropine and/or implanted pacemaker if symptomatic bradycardia or heart block.
Supraventricular tachycardia	First onset is rare. Previously diagnosed tachycardia may aggravate.	First choice: vagal stimulation manoeuvres. Escalating doses of adenosine up to 18-24 mg. Verapamil second line. Propranolol or metoprolol are also appropriate. If haemodynamically unstable it should be electrically cardioverted.
Atrial Fibrillation	Rare, usually secondary to heart disease or metabolic disturbances.	Cases of lone AF use iIbutilide or flecainide to sinus rhythm conversion or cardioselective beta-blocker drug alone or in combination with digoxin to control ventricular rate; anticoagulation therapy is not necessary. Perform electrical cardioversion if haemodynamically unstable. If increased thrombo-embolic risk, prophylaxis is recommended in high risk patients.
Ventricular tachycardia	Rare in the absence of organic heart disease. Physical or psychological stress might precipitate. Polymorphic VT can degenerate into ventricular fibrillation.	If stable, lidocaine, sotalol or procainamide. Amiodarone only if VT persists. Beta-blockers are the choice for idiopathic catecholamine-sensitive VT. If unstable, it must undergo emergent electrical cardioversion. ICD implantation must be considered in cases of therapy-resistant VT.

AF: atrial fibrillation; ICD: implantable cardioverter-defibrillator; VT: ventricular tachycardia.

Table 8. European Society of Cardiology (ESC) (2011).[33] Recommendations for the management of arrhythmias during pregnancy.

Recommendations	Class[a]	Level[b]
Management of supraventricular tachycardia		
For acute conversion of paroxysmal SVT, vagal manoeuvre followed by IV adenosine is recommended.	I	C
Immediate electrical cardioversion is recommended for acute treatment of any tachycardia with haemodynamic instability.	I	C
For long-term management of SVT oral digoxin[c] or metoprolol/propranolol[c,d] is recommended.	I	C
For acute conversion of paroxysmal SVT, IV metoprolol or propranolol should be considered.	IIa	C
For long-term management of SVT, oral sotalol[e] or flecainide[f] should be considered if digoxin or a β-blocking agents fails.	IIa	C
For acute conversion of paroxysmal SVT, IV verapamil may be considered.	IIb	C
For long-term management of SVT, oral propafenone[f], or procainamide may be considered as a last option if other suggested agents fail and before amiodarone is used.	IIb	C
For long-term management of SVT, oral verapamil[c] may be considered for rate regulation if the other AV nodal-blocking agents fail.	IIb	C
Atenolol[d] should not be used for any arrhythmia.	III	C
Management of ventricular tachycardia		
The implantation of an ICD, if clinically indicated, is recommended prior to pregnancy but is also recommended whenever indicated, during pregnancy.	I	C
For long-term management of the congenital long QT syndrome, β-blocking agents are recommended during pregnancy and also postpartum when they have a major benefit.	I	C
For long-term management of idiopathic sustained VT oral metoprolol[c,d], propranolol[c,d] or verapamil[c,f] is recommended.	I	C
Immediate electrical cardioversion of VT is recommended for sustained, unstable, and stable VT.	I	C
For acute conversion of VT that is sustained, haemodynamically stable, and monomorphic, IV sotalol or procainamide should be considered.	IIa	C
Implantation of permanent pacemakers or ICDs (preferably one chamber) should be considered with echocardiographical guidance, especially if the fetus is beyond 8 weeks gestation.	IIa	C
For acute conversion of VT that is sustained, monomorphic, haemodynamically unstable, refractory to electrical cardioversion or not responding to other drugs, IV amiodarone[e] should be considered.	IIa	C
For long-term management of idiopathic sustained VT oral sotalol[e], flecainide[f], propafenone[f] should be considered if other drugs fail.	IIa	C
Catheter ablation may be considered in the case of drug-refractory and poorly tolerated tachycardias.	IIb	C

Taken and adapted from ESC Guidelines on the management of cardiovascular diseases during pregnancy.[33]

[a] Class of recommendation.

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy. Class IIb: Usefulness/efficacy is less well established by evidence/opinion. Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

[b] Level of evidence.

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses. Level of Evidence B: Data derived from a single randomized clinical trial or large non-randomized studies. Level of Evidence C: Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

[c] AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG.

[d] β-blocking agents should be used with caution in the first trimester.

[e] Class III drugs should not be used in cases with prolonged QTc.

[f] Consider AV nodal blocking agents in conjunction with flecainide and propafenone for certain atrial tachycardias.

AV: atrioventricular; ECG: electrocardiogram; ESC: European Society of Cardiology; ICD: implantable cardioverter-defibrillator; IV: intravenous; SVT: supraventricular tachycardia; VT: ventricular tachycardia.

Table 9. Clinically significant AF episode (with hospitalization or medical treatment) by trimester of onset.[24]

	Rate per 100000 pregnancies (95% CI)	OR (95% CI)	P-value
First trimester	3.4 (1.2-5.6)	1	
Second trimester	6.8 (3.7-9.9)	2.0 (0.9-5.1)	0.12
Third trimester	11.0 (7.0-15.0)	3.2 (1.5-7.7)	**0.002**
Postpartum (6 months)	1.5 (0.03-3.0)	0.4 (0.1-1.6)	0.26

P value: 2-sided P value calculated using Fisher's exact test.

Statistically significant values are in bold.

AF: atrial fibrillation or atrial flutter; OR: odds ratio.

AF episodes were statistically significant higher during the third trimester.

Taken and adapted form Lee et al (2016).[24]

Table 10. Overview of the existing literature on ICD therapy in pregnancy and problems with ICD therapy during pregnancy.

A - Overview of the existing literature on ICD therapy in pregnancy. [45]

Study/ Year	No of pregnancies	Age (mean)	Structural heart disease – n (%)	Pre-pectoral ICDs – n (%)	Endocardial leads – n (%)	Device-related complication	No of women who experienced ICD shocks	Fetal consequences of ICD shocks
Natale et al. (44)/1997	51	30	14 (32)	2 (5)	14 (32)	Migration of an abdominal generator, pericarditis related to epicardial patches	11	None
Schuler et al. (45)/2012	19	33	10 (71)	13 (93)	14 (100)	None	0	None
Miyoshi et al. (49)/2013	6	28	3 (50)	6 (100)	6 (100)	None	0	-
Boulé et al. (42)/2014	20	28	7 (58)	12 (100)	12 (100)	None	2	One miscarriage may have been provoked by ICD shocks (4 weeks gestation)

B - Problems with ICD therapy during pregnancy.[44]

Lead fracture, device-related thrombus and device infection
Stress on the epicardial or transvenous system increases as the diaphragm elevates and the abdominal girth expands secondary to fetal growth
Inappropriate ICD shock
Due to increased sinus rate, supraventricular tachyarrhythmia
Postpartum period
Additional caution required for shock after delivery
Device programming
Vaginal delivery: full therapy mode is recommended Caesarean section: monitor only is recommended

A - ICD: implantable cardioverter-defibrillator.

Taken and adapted from Boule et al (2014).[45]

B - ICD: implantable cardioverter-defibrillator.

Taken from Ishikawa (2013).[44]

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Appendix

Appendix 1 License for Figure 1 of the manuscript “Pregnancy Cardiac Arrhythmias” utilization. From the original article Vaidya VR, Arora S, Patel N, et al. Burden of Arrhythmia in Pregnancy. Circulation. 2017;135(6):619-21.

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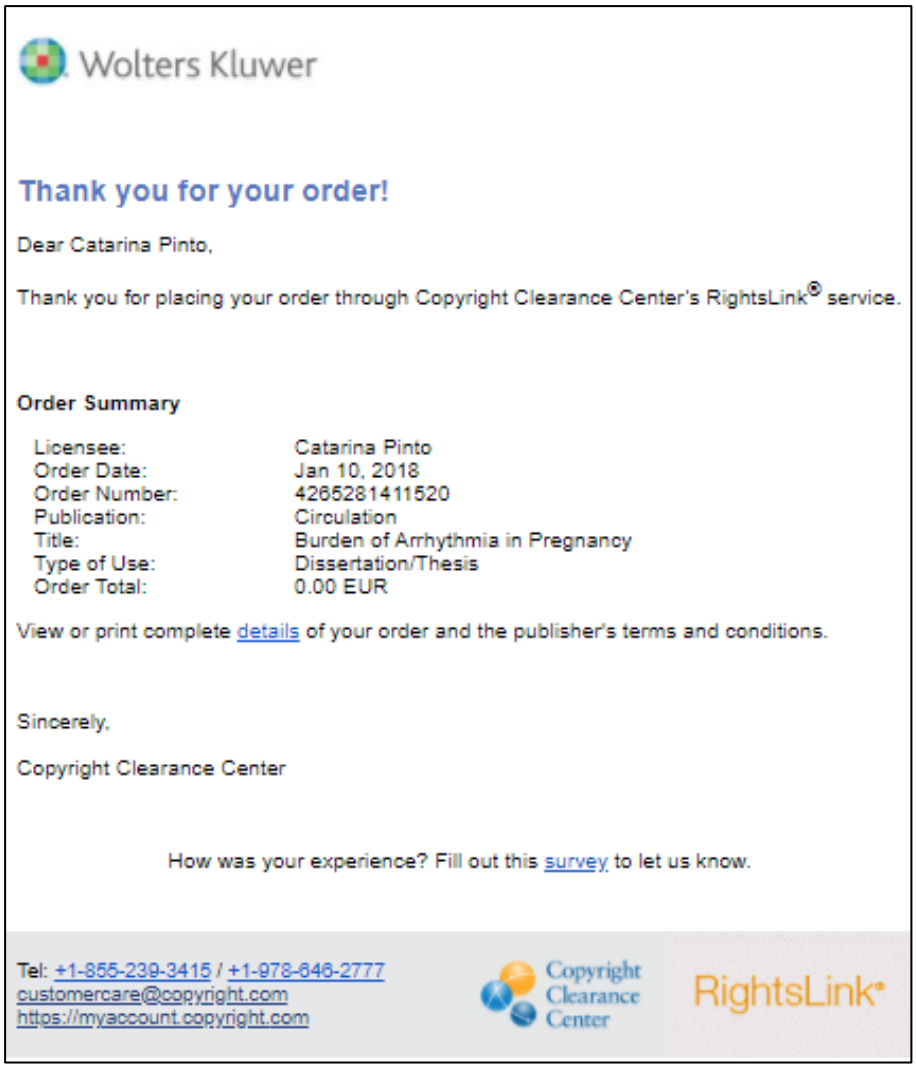

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Material electrónico: Artigo de revista em formato electrónico. *Exemplo:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts it an advisory role. Am J Nurs. [serie na internet.] 2002 Jun citado 12 Ago 2002:102(6): [aprox. 3] p. Disponível em: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

. A Bibliografia será enviada como texto regular, nunca como nota de rodapé. Não se aceitam códigos específicos dos programas de gestão bibliográfica.

1. Figuras

As figuras correspondentes a gráficos e desenhos são enviadas no formato TIFF ou JPEG de preferência, com uma resolução nunca inferior a 300 dpi e utilizando o negro para linhas e texto. São alvo de numeração árabe de acordo com a ordem de entrada no texto.

- A grafia, símbolos, letras, etc, deverão ser enviados num tamanho que, ao ser reduzido, os mantenha claramente legíveis. Os detalhes especiais deverão ser assinalados com setas contrastantes com a figura.
- As legendas das figuras devem ser incluídas numa folha aparte. No final devem ser identificadas as abreviaturas empregues por ordem alfabética.
- As figuras não podem incluir dados que dêem a conhecer a proveniência do trabalho ou a identidade do paciente. As fotografias das pessoas devem ser feitas de maneira que estas não sejam identificadas ou incluir-se-á o consentimento por parte da pessoa fotografada.

Tabelas

São identificadas com numeração árabe de acordo com a ordem de entrada no texto.

Cada tabela será escrita a espaço duplo numa folha aparte.

- Incluem um título na parte superior e na parte inferior são referidas as abreviaturas por ordem alfabética.
- O seu conteúdo é auto-explicativo e os dados que incluem não figuram no texto nem nas figuras.

2. Artigos de Revisão

Nº máximo de palavras do artigo sem contar com o resumo e quadros- 5.000
Nº máximo de palavras do Resumo - 250
Nº máximo de Figuras - 10
Nº máximo de quadros - 10
Nº máximo de ref. bibliográficas - 100

3. Cartas ao Editor

Devem ser enviadas sob esta rubrica e referem-se a artigos publicados na Revista. Serão somente consideradas as cartas recebidas no prazo de oito semanas após a publicação do artigo em questão.

- Com espaço duplo, com margens de 2,5 cm.
- O título (em português e em inglês), os autores (máximo quatro), proveniência, endereço e figuras devem ser especificados de acordo com as normas anteriormente referidas para os artigos originais.
- Não podem exceder as 800 palavras.
- Podem incluir um número máximo de duas figuras. As tabelas estão excluídas.

4. Casos Clínicos

Devem ser enviados sob esta rubrica.

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder 10 palavras

Os autores (máximo oito) proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.

O texto explicativo não pode exceder 3.000 palavras e contem informação de maior relevância. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.

Contêm um número máximo de 4 figuras e pode ser enviado material suplementar, como por exemplo vídeoclips.

5. Imagens em Cardiologia

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder oito palavras
- Os autores (máximo seis), proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.
- O texto explicativo não pode exceder as 250 palavras e contem informação de maior relevância, sem referências bibliográficas. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.
- Contêm um número máximo de quatro figuras.

6. Material adicional na WEB

A Revista Portuguesa de Cardiologia aceita o envio de material electrónico adicional para apoiar e melhorar a apresentação da sua investigação científica. Contudo, unicamente se considerará para publicação o material electrónico adicional directamente relacionado com o conteúdo do artigo e a sua aceitação final dependerá do critério do Editor. O material adicional aceite não será traduzido e publicar-se-á electronicamente no formato da sua recepção.

Para assegurar que o material tenha o formato apropriado recomendamos o seguinte:

	Formato	Extensão	Detalhes
Texto	Word	.doc ou docx	Tamanho máximo 300 Kb
Imagem	TIFF	.tif	Tamanho máximo 10MB
Audio	MP3	.mp3	Tamanho máximo 10MB
Vídeo	WMV	.wmv	Tamanho máximo 30MB

Os autores deverão submeter o material no formato electrónico através do EES como arquivo multimédia juntamente com o artigo e conceber um título conciso e descritivo para cada arquivo.

Do mesmo modo, este tipo de material deverá cumprir também todos os requisitos e responsabilidades éticas gerais descritas nessas normas.

O Corpo Redactorial reserva-se o direito de recusar o material electrónico que não julgue apropriado.

ANEXO I

DECLARAÇÃO

Declaro que autorizo a publicação do manuscrito:

Ref.ª .....

Título .....

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do qual sou autor ou c/autor.

Declaro ainda que presente manuscrito é original, não foi objecto de qualquer outro tipo de publicação e cedo a inteira propriedade à Revista Portuguesa de Cardiologia, ficando a sua reprodução, no todo ou em parte, dependente de prévia autorização dos editores.

Nome dos autores:

.....

.....

Assinaturas:

ANEXO II

Símbolos, abreviaturas de medidas ou estatística

Designação	Português	Inglês
Ampere	A	A
Ano	ano	yr
Centímetro quadrado	cm_2	cm_2
Contagens por minuto	cpm	cpm
Contagens por segundo	cps	cps
Curie	Ci	Ci
Electrocardiograma	ECG	ECG
Equivalente	Eq	Eq
Grau Celsius	°C	°C
Grama	g	g
Hemoglobina	Hb	Hb
Hertz	Hz	Hz
Hora	h	h
Joule	J	J
Litro	L ou L	l ou L
Metro	m	m
Minuto	min	min
Molar	M	M
Mole	mol	mol
Normal (concentração)	N	N
Ohm	Ω	Ω
Osmol	osmol	osmol
Peso	peso	WT
Pressão parcial de CO_2	pCO_2	pCO_2
Pressão parcial de O_2	pO_2	pO_2
Quilograma	kg	kg
Segundo	s	sec
Semana	Sem	Wk
Sistema nervoso central	SNC	CNS
Unidade Internacional	UI	IU
Volt	V	V
Milivolt	mV	mV
Volume	Vol	Vol
Watts	W	W
Estatística:		
Coeficiente de correlação	r	r
Desvio padrão (standard)	DP	SD
Erro padrão (standard) da média	EPM	SEM
Graus de liberdade	gl	df
Média	χ	χ
Não significativa	NS	NS
Número de observações	n	n
Probabilidade	p	p
Teste «t» de Student	teste t	t test