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Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia in Pregnancy: Literature Review and Case Update

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Abstract

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an autosomal dominant condition that may predispose patients to life-threatening arrhythmia, posing a potentially significant cardiac risk in pregnancy. Management of this condition is performed on a case-to-case basis as research is limited.

A 28 year old woman was diagnosed with Arrhythmogenic right ventricular cardiomyopathy/dysplasia following genetic screening performed after a sudden sporting-induced collapse of her brother at age 21, at which point a prophylactic implantable cardioverter defibrillator (ICD) was placed. She became pregnant after the placement of the ICD and underwent a spontaneous miscarriage at 10 weeks gestation, which was successfully managed medically. ARVC/D is uncommonly considered alongside pregnancy; therefore, patients are managed individually, which requires a thorough understanding of current strategies.

A literature review was performed using PubMed to assess current knowledge of ARVC/D in pregnancy.

Although limited, published case reports and few retrospective cohort and systematic reviews conclusively describe safe pregnancy in mothers with Arrhythmogenic right ventricular cardiomyopathy/dysplasia. In the majority of cases, pregnancy is safe to progress to term and vaginal delivery is preferred, where Caesarean section is only indicated in cases of obstetric complications. Prophylactic ICD placement is the first-line management to prevent arrhythmia; flecainide or radio-ablation are the preferred second line treatments in the absence of an ICD. To reduce the risk of arrhythmia, beta-blockers should be continued throughout the pregnancy.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia poses a cardiac complication that requires unique management and counselling. Although the majority of cases will result in vaginal delivery, safe management of pregnancy includes frequent cardiac monitoring of the mother and health of the foetus as well as precautions regarding delivery and genetic counselling.

Keywords: Arrhythmogenic right ventricular cardiomyopathy; Pregnancy; Women

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Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an autosomal dominant condition associated with fibrofatty replacement of right ventricular myocardium [1]. ARVC/D has been implicated as a cause of sudden death among young athletes, therefore the role of this condition along with the cardiovascular changes of pregnancy must be ascertained [2]. The majority of women diagnosed with ARVC/D present with symptomatic palpitations in child-bearing years, representing a rare clinical challenge when considered along with pregnancy [3].

The fundamental pathology lies in desmosomal proteins, which are responsible for maintaining the integrity of cell-to-cell adhesion and molecular communication. There have been five identified desmosomal genes, mutations of which are associated

with ARVC/D, specifically: plakophilin-2, desmoglein-2, desmoscollin-2, desmoplakin and junctional plakoglobin with variable penetrance and incomplete expression [4-6]. Familial genetic testing has been described as the second most common means to attain a diagnosis early, and has opened the door to earlier introduction of safe pre-natal, antenatal and post-natal management [3].

As ARVC/D progresses, the remodelling of the right ventricle leads to a progressive dilated cardiomyopathy and subsequent heart failure, involvement of the left ventricle and severe ventricular arrhythmias [5-7] Significant cardiac events in ARVC/D include cardiac arrest due to ventricular fibrillation and sustained ventricular tachycardia, which may result in sudden cardiac death, as well as the progression to heart failure. In pregnancy, the threat of death is uncommon, however pregnancy increases the risk ventricular arrhythmias and heart failure [3,8].

In the case presented here, a 28-year-old woman underwent spontaneous miscarriage at 10 weeks' gestation, which was subsequently managed medically with no complications. She was previously diagnosed with ARVC/D by genetic testing following the sudden sporting-induced collapse of her brother. A prophylactic Implantable Cardioverter Defibrillator (ICD) was placed at the time of diagnosis and the patient was commenced on bisoprolol.

Due to the rare nature of this condition, pregnancies are managed on a case-by-case basis. Therefore, a thorough understanding of the possible complications of ARVC/D in pregnancy is essential to prepare for optimal outcomes. The majority of research presented on this topic is encompassed by case reports, with a number of recent retrospective cohort analyses containing a larger sample size. The purpose of this review is to outline pregnancy risks and effective management options for women with ARVC/D, based on available evidence in the literature.

Literature Review

A literature review of the present research including case reports, reviews and primary research was conducted using PubMed. Consent was obtained from the patient presented in this case report.

Diagnosis and risk classification

The care of pregnancy complicated by ARVC/D begins from diagnosis of the condition. Clinically, diagnosis is made using the 2010 Task Force Criteria, which was revised from the original version presented in 1994. The Task Force Criteria consists of six categories, each with major and minor diagnostic criteria. These six categories include: global or regional dysfunction and structural alterations, tissue characterization of the wall, repolarization abnormalities, depolarization/conduction abnormalities, arrhythmias and family history. Major and minor criteria for each category are outlined in Appendix A. The new 2010 Task Force criteria for diagnosis largely include new imaging criteria for structural alterations by 2D echo, by MRI or by RV angiography. Furthermore, the clinical elements of the presented criteria enable prediction of disease severity, which may inform on risk of cardiac events [7]. Based on the Task Force Criteria, the patient considered in this case was diagnosed following the sudden collapse of her brother who was diagnosed with ARVC/D with gene testing. She subsequently received genetic testing, along with members of her family, which detected a relevant genetic mutation.

Genetic testing has led to early detection of the possibility of ARVC/D. However, clinical rather than the genetic features, have a greater impact on the severity of disease and associated arrhythmia outcomes [9]. Therefore, assessing clinical risk is an essential component to discern the need for anti-arrhythmic medication, or ICD implantation. In pregnancy in particular, there are three main scoring systems that may predict cardiovascular complications including the CARPREG (Cardiac Disease in Pregnancy) and CARPREG II, ZAHARA (Zwangerschap bij Aangeboren HARtAfwijking) and mWHO (modified World Health Organization) scores.

The mWHO score focuses on risk stratification of those with heart failure or atrial fibrillation. It has the advantage of a large global population cohort [10]. The CARPREG score includes a number of clinical predictors that, if present, are associated with an elevated risk of a cardiac event including worsening of heart failure, symptomatic tachyarrhythmia or brady arrhythmia requiring treatment, stroke, cardiac arrest or cardiac death [11]. The CARPREG score was revised in 2018 to include additional criteria specific to structural heart disease detectable with echocardiography. The original CARPREG score was developed using a patient population that consisted largely of congenital heart disease, which may poorly extrapolate to cardiomyopathies and ARVC/D. The ZAHARA score also focuses on women with congenital heart disease and corresponding risk of cardiac events in pregnancy [12]. A retrospective cohort analysis detected increased predictive value of the CARPREG II score over the ZAHARA and mWHO in pregnant women with cardiomyopathies [13,14]. Use of a risk stratification system may assist in detecting the likelihood of developing an arrhythmia or cardiac event, and as such require closer monitoring at a tertiary care center throughout pregnancy.

When considering cardiac complications, the antepartum, intrapartum and post-partum periods must be managed separately, as the risks in each stage of pregnancy differs. Risk of arrhythmia is highest in the second trimester, where risk of progressive heart failure is identified to be highest in the third trimester and post-partum period [8,14].

Pre-conception

Optimizing cardiac function prior to pregnancy with antiarrhythmic therapy or ICD implantation, and maintaining this regimen throughout the pregnancy is associated with positive outcomes for the mother and the baby [3,15]. Sudden cardiac death may be an outcome in pregnancy if the diagnosis of ARVC/D is unknown and treatment is not commenced, as documented by Vadysinghe, et al. [16]. Pre-conception assessment includes echocardiogram to discern structural and functional capability of the heart, including

24-hours Holter monitor, ECG and cardiac MRI, if available [17]. Patients undergoing Task Force criteria assessment will receive these investigations to inform on clinical diagnosis of ARVC/D and receive specialist cardiologist follow-up prior to pregnancy counselling.

Antepartum

For cases of ARVC/D diagnosed prior to pregnancy, assessment of the severity of the condition is essential for adequate counselling regarding the patient's decision to undergo pregnancy. Reduced left ventricular ejection fraction has been reported by Wu, et al. to increase all-cause mortality [18]. Güdücü, et al. recommended avoiding pregnancy in cases of severe ARVC/D or evidence of congestive heart failure; however evidence regarding the severity and degree of heart failure has not been reported [19]. Hodes, et al. reported 82% of pregnancies in a sample of 39 singleton pregnancies lead to a healthy, safe pregnancy and delivery with no ventricular arrhythmia or heart failure events. However, regular monitoring of possible cardiac outcomes, including arrhythmia and progression to heart failure, is essential during the course of the pregnancy. Antepartum monitoring is best conducted using a multidisciplinary team approach, in particular an obstetrician and/or maternal-fetal medicine specialist to manage obstetric care and a cardiologist to manage cardiac care. Consultation with anaesthesia to discuss the labour plan and possible anaesthetic outcomes, this team-based approach should be continued throughout labour and into the post-partum period.

The development of a ventricular arrhythmia during pregnancy most commonly tachyarrhythmia or fibrillation, may be managed medically, through cardioversion or catheter ablation. Medical management has been successful with bisoprolol and flecainide [3]. In most cases where symptoms worsened, but were not classified as a severe cardiac event, management was successful with titration of current anti-arrhythmic [8]. This further supports the role of a medical cardiologist in management of ARVC/D complications, along with adequate relay of information to obstetrician in order to ensure optimal fetal health.

With the risk of progression to heart failure being greatest in the 3rd trimester and post-partum, symptoms of cardiac overload should be closely monitored by the cardiologist as well as the obstetrician. Those with severe right ventricular structural disease were more likely to develop heart failure, a finding that may be detected following early risk assessment. Treatment of cardiac insufficiency in pregnancy includes use of diuretics and digoxin. In acutely severe cases, the decision to progress to delivery by induction or caesarean may be imminent [8].

In cases where the diagnosis of ARVC is made during pregnancy, implanting an ICD during pregnancy has been associated with good outcomes and a low rate of complications [20,21]. Furthermore, commencing beta blocker therapy has been shown to be safe [18]. Beta blocker use during pregnancy continuously depicts increased rates of intrauterine growth restriction, which may necessitate serial growth scans [22].

Labour

In most cases, pregnancies are carried to term, with no increased risk of pre-term delivery related to ARVC/D. Vaginal delivery is generally safe with cardiac monitoring, with the decision to deliver by C-section based on obstetric indications [3]. It is recommended that intra-partum continuous cardiac monitoring should be utilized by ECG, particularly in cases where an ICD has not been placed. Induction may be required and has been deemed safe in order to ensure timely multidisciplinary management and cardiac team availability [17]. Induction of labour has been deemed safe with the use of continuous cardiac monitoring. If urgent C-section is required, the use of general anaesthesia has been reportedly safe, with good outcomes [19,23]. If proceeding through induction, the use of continuous fetal monitoring would be indicated.

Post-partum

The impact of pregnancy on the cardiovascular system persists until 6 weeks post-partum; therefore the majority of research consists of 6-week follow-up. Importantly, there has been no link between pregnancy and progression of ARVC/D [8,24]. Beta blocker therapy during pregnancy is associated with a low infant birth weight and IUGR in some cases [22]. Additionally, a higher risk of SIDS and SCD has been detected in infants born to mothers with ARVC [3]. This suggests the importance of genetic testing and potential inheritance of susceptible genes.

Discussion and Conclusion

ARVC/D is a rare cardiac condition that presents a unique challenge when considered along with pregnancy. Limited published research on this topic has prompted a review of the existing evidence to warrant for sound recommendations for the management of pregnancy on a background of ARVC/D. In most cases, pregnancy is safe to progress to term and vaginal delivery is recommended. As each individual patient may progress differently, an adequate pre-conception risk assessment, multidisciplinary management and regular antepartum monitoring for severe cardiac events are essential. Ventricular arrhythmia and heart failure are acutely severe events that may complicate the progression of pregnancy; however, evidence suggests these may be managed acutely, with the possibility to continue the pregnancy to term. The decision to deliver is weighed against the gestation of the pregnancy, however most emergency C-sections, or preterm deliveries presented have been due to obstetric, rather than cardiac indications.

Definite diagnosis can be made with

2 Major criteria or

1 Major criteria+2 minor criteria

4 Minor criteria

Borderline diagnosis can be made with

1 Major criteria and 1 minor criteria

3 Minor criteria

Possible diagnosis can be made with

1 Major criteria or

2 Minor criteria

Recommendations

As the severity of ARVC/D may be different in each and every patient, it is essential to risk-stratify and manage pregnancy individually with a multidisciplinary team. However, certain recommendations should be followed based on available evidence that outlines safe pregnancy care resulting in good outcomes for both mother and child. Primarily, ARVC/D diagnosis before pregnancy is ideal, as it enables the establishment of an adequate ARVC/D management strategy with the use of anti-arrhythmic medication or placement of an ICD. This medical strategy should be continued into and throughout pregnancy following a full pre-conception cardiac assessment. In the event of a ventricular arrhythmia during pregnancy, treatment with abortive antiarrhythmic, catheter ablation and ICD placement has been reported to be safe and effective. In rare cases, ARVC/D may present during pregnancy. In these patients, commencing beta blocker therapy during pregnancy has resulted in good outcomes, and ICD placement may be considered if the risk of ventricular arrhythmia is high. Vaginal delivery is generally safe, where epidural anaesthesia should be considered in order to reduce the degree of cardiovascular stress. Furthermore, induction of labour may allow for timely delivery with the cardiac team, obstetrician, paediatrician and anaesthetist on site. If IUGR is detected, delivery at a care centre that is equipped with a neonatal intensive care unit should be considered. Monitoring until 6 weeks post-partum should be strongly encouraged to ensure the cardiovascular system returns to a stable baseline. Importantly, pregnancy, and number of subsequent pregnancies, has not been shown to affect progression of the severity of ARVC/D. Finally, genetic counselling should be provided, and a multidisciplinary team created to include maternal-fetal medicine specialist, general obstetrician, anaesthesiologist, cardiologist, and neonatology for the individualized care of each patient.

Despite limitations to the quantity of available evidence, due to the rare nature of ARVC/D and pregnancy, most research presented to date supports safe pregnancy and delivery. Despite optimization of risk assessment tools, the uncertainty regarding predictability of severe cardiac outcomes calls for chronic, sustained treatment of ARVC/D, especially during pregnancy. Cohort analyses will inevitably contain evidence including patients taking treatment during pregnancy, with little comparable control arm evidence. Further research may focus on increasing sample size and optimizing medical therapy during pregnancy, in order to reduce the incidence of fetal growth restriction due to beta-blocker therapy, and worsening of symptoms.

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