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Pregnancy and newborn outcomes in arrhythmogenic right ventricular cardiomyopathy/dysplasia

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ABSTRACT

Introduction: The prognosis of pregnancy in patients with Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia (ARVC/D) is poorly documented. The aim of this study is to assess the cardiac risks during pregnancy and the impact of ARVC/D on fetuses/neonates/children.
Methods: We included all ARVC/D women with a history of pregnancy from the ARVC/D Pitié-Salpêtrière registry. Cardiac and obstetrical events having occurred during pregnancy/delivery/post-partum periods and neonatal data/follow-up were collected.
Results: Sixty pregnancies in twenty-three patients were identified between 1968 and 2016. Only two major non-fatal cardiac events (one sustained non-documented tachycardia and one ventricular tachycardia) were recorded during pregnancy in two different mothers (3% of pregnancies, 9% of mothers). None occurred during delivery or in the postpartum period. No mother developed heart failure. Beta-blocker therapy during pregnancy ($n = 15$) was associated with lower birthweight (2730 vs 3400 g, $p = 0.004$). Only two preterm deliveries occurred, unrelated to cardiac condition. Caesarean section was performed in 13% of cases. Premature sudden-death occurred in 10% ($n = 5$) of children before 25 years-old including two in the first year of life.
Conclusion: ARVC/D is associated with a low rate of major cardiac events during pregnancy and vaginal delivery appears safe. The risk of sustained ventricular arrhythmia seems poorly predictable and supports the continuation of beta-blockers during pregnancy. Major cardiac events were frequent in childhood, justifying close cardiac monitoring.

1. Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) is a rare inherited cardiomyopathy characterized by fibrofatty tissue replacement of myocardium, predominantly in the right ventricle [1]. ARVC/D is responsible for frequent right ventricular arrhythmias and can lead to sudden cardiac death (SCD) [2] or progress to heart failure caused by right ventricular or biventricular dysfunction [2]. Pregnancy is a situation at risk for women with cardiomyopathy [3–5]. Specific risk and management of pregnancy in affected ARVC/D women is insufficiently documented, with mostly small case-series and case-reports [6–9]. Recently, a large case-series from the Dutch/Johns Hopkins registry reported a low rate of major cardiac events during pregnancy [10]. The aim of this study was to assess the cardiac, as well as obstetrical, fetal, neonatal, and childhood risk of complications in women with documented ARVC/D and their children.

We conducted a large retrospective study including all consecutive ARVC/D women with a history of pregnancy from a single tertiary care center (Pitié-Salpêtrière University Hospital).

2. Material and methods

2.1. Study design and population

All women followed-up in our tertiary care center (Pitié Salpêtrière University Hospital) with an ARVC/D diagnosis between 1984 and 2015 were identified. ARVC/D diagnosis was made by local multidisciplinary consensus experts. Clinical data were reviewed by two independent experts and diagnosis was assessed according to the 2010 international

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Task Force criteria for the study [11]. All subjects with a history of pregnancy were included in the study.

According to our institution's policy, no authorization approval from our Institutional Committee on Human Research was required for this retrospective study. All women included in the study gave their written consent.

2.2. Data collection and definitions

Patient characteristics were obtained from medical records: clinical information, medications, cardio-vascular symptoms, 12 lead electrocardiogram, 24 h Holter-monitoring, exercise-stress testing, signal-averaged electrocardiogram, prior catheter ablation, implantable cardioverter defibrillator (ICD) and family history. Morphological abnormalities were assessed through echocardiography, cardiac Magnetic Resonance Imaging (MRI) and right ventricular (RV) contrast angiography, when available. RV dysfunction was defined by RV ejection fraction <45% by contrast angiography or MRI or right fractional area change (RFAC) <40%. Left ventricular (LV) involvement was defined as LV ejection fraction <50%. RV fractional area change (RFAC) was measured in the apical four-chamber view and left ventricular ejection fraction (LVEF) was assessed by the biapical Simpson disk method. When ARVC/D diagnosis was diagnosed before pregnancy, clinical data used were those collected at the time of the first pregnancy. Otherwise, clinical data used were those collected at the time of the diagnosis (i.e. after pregnancy).

Data on pregnancy and events in children were collected retrospectively by written questionnaire. Subjects were asked if the following events occurred during pregnancy, delivery and post-partum periods: cardiac symptoms (including syncope, heart failure and arrhythmic events), anti-arrhythmia drug therapy during pregnancy, obstetrical events during pregnancy, delivery and post-partum characteristics, unplanned admissions, and breastfeeding. Preterm births were defined by delivery <37 weeks of gestation. We also asked patients for any spontaneous miscarriages, abortion, terminations of pregnancy, and ectopic pregnancies. We collected by written questionnaire the following data on newborns: Apgar score at 1 and 5 min, weight at birth, any cardiovascular events after birth until age of 25, presence of malformations. Sudden Infant Death Syndrome (SIDS) was defined by unexplained sudden death occurring <1-year-old.

2.3. Genetic analysis

A mutation screening of desmosomal genes *PKP2*, *DSG2*, *DSP*, *JUP* and *DSC2* was performed when available by Sanger Sequencing (Big Dye Terminator® chemistry, Perkin Elmer©) on an ABI 3830 DNA sequencer (PE Applied Biosystems©). A genetic variant was considered as a causal mutation on the basis of (i) variant with a frequency <0.1% in the EXAC database (http://exac.broadinstitute.org) (ii) radical mutations (nonsense mutation, frame shift mutation), or (iii) in the presence of a missense mutation, when predicted pathogenous by three appropriate softwares (Polyphen, SIFT, Align GVGD).

2.4. Statistical analysis

Continuous variables are expressed as median [min–max] and were compared across groups using the Mann-Whitney *U* test with the SPSS 22.0 software. Categorical variables are reported as n (%) and were compared using the Fisher exact test. *P*-value <0.05 defined significance.

3. Results

3.1. Mothers' characteristics at ARVC/D diagnosis

Twenty-seven women with ARVC/D diagnosed between 1984 and 2015 and a history of pregnancy were identified. Among them, twenty-three accepted to be included in the study, four patients declined to answer the questionnaire. Clinical data of subjects are detailed in Tables 1 and 2. Mean age at ARVC/D diagnosis was 38 (range 24–63) years. Twenty (87%) subjects had a definite diagnosis according to Task Force criteria, three had a borderline diagnosis (including one with a *PKP2* mutation and one with a *DSC2* mutation) [11]. Most women (70%) were symptomatic at ARVC/D diagnosis, mostly with palpitations (details in Tables 1 and 2). Mean age at onset of symptoms was 31 years, e.g. 10 ± 11 years before ARVC/D diagnosis. Most patients displayed ventricular arrhythmia, mostly premature ventricular contractions (PVCs) ($n = 17$). Only three (patients 16, 19 and 23, Table 2) had a history of ventricular tachycardia (VT) and one had a history of aborted cardiac arrest (patient 8, Table 2) at diagnosis. A family history of sudden infant death syndrome (SIDS) was present in three patients (13%). Genetic data were available in 19 patients. 47% of mothers ($n = 9/19$) carried a mutation in a desmosomal gene: six carried a *PKP2*, two a *DSG2* and one a *DSC2* mutation, ten had a negative genetic screening.

Table 1
Clinical characteristics of mothers.

	ARVC/D mothers ($n = 23$) Median [min–max] or N (%)
Diagnosis	
Age at diagnosis (years)	38 [24–63]
Circumstances of diagnosis	
Familial screening	8 (35%)
Non-fatal cardiac arrest	1 (4%)
Sustained VT	2 (9%)
Symptomatic PVC	12 (52%)
Presence of a desmosomal mutation ($n = 19$)	9 (47%)
ARVC/D diagnosis according to 2010 TF criteria	20 (87%)
Family history	
SIDS	3 (13%)
SCD	9 (39%)
ARVC/D in 1st-degree relative	10 (43%)
Clinical data	
Symptoms	16 (70%)
Age at first symptoms	28 [20–51]
Time between 1st symptoms and diagnosis (years)	7 [0 − 33]
Ventricular arrhythmias	
SCD	1 (4%)
Sustained VT	3 (13%)
>200 PVC/24 h	17 (74%)
ICD during follow-up	4 (17%)
ECG	
TWI > V2	9 (39%)
Epsilon wave	3 (13%)
Parietal block V1-V2	7 (30%)
Complete RBBB	3 (13%)
Positive SA-ECG ($n = 22$)	12 (55%)
Imaging	
RV dysfunction (RFAC < 40% and/or RVEF < 45% MRI)	9 (39%)
LV dysfunction (LVEF < 50%)	3 (14%)

ICD: implantable cardioverter defibrillator; LV: left ventricle; PVC: premature ventricular contractions; RBBB: right bundle branch block; RV: right ventricle; SCD: sudden cardiac death; SIDS: Sudden Infant Death Syndrome, TWI: T wave inversion; VT: ventricular tachycardia.

3.2. Pregnancy characteristics

Sixty pregnancies were held between 1968 and 2016 in 23 women: 50 (83%) were completed, six (10%) led to early miscarriages (<12 weeks of gestation), two were ectopic pregnancies and two were terminated for trisomy 21 (Table 3 and Fig. 1). In vitro fertilization was performed for three pregnancies. Mean maternal age at the time of pregnancy was 29.8 ± 5.2 years. Eleven (18%) pregnancies occurred after ARVC/D diagnosis. Among the 49 pregnancies that occurred before ARVC/D diagnosis, the mean time between pregnancy and diagnosis was 16 ± 11 years. However, some of these undiagnosed mothers already had evidence of ventricular arrhythmia during pregnancy ($n = 4$) or were symptomatic with palpitations or dyspnea that secondarily led to ARVC/D diagnosis ($n = 12$, details in Supplementary Table). In four cases, ARVC/D diagnosis was performed during or just after pregnancy because of ventricular arrhythmias identified during pregnancy: one had a first episode of sustained VT during pregnancy (patient 16, Table 2 and Supplementary Table) and three were diagnosed with PVCs during pregnancy (patient 1, 6 and 13, Table 2 and Supplementary Table).

Seventeen (28%) pregnancies took place on anti-arrhythmic (AAR) therapy: seven (12%) on beta-blockers alone, eight (13%) on flecainide/beta-blockers association and two (3%) on flecainide alone. Beta-blockers used were bisoprolol ($n = 6$), acebutolol ($n = 1$), propranolol ($n = 1$), nadolol ($n = 1$), betaxolol ($n = 3$), sotalol ($n = 1$) and undocumented in two cases. AAR therapy was prescribed because of PVC ($n = 10$), PVC with history of SCD ($n = 1$), VT ($n = 3$), PVC with undocumented tachycardia ($n = 2$) and for palpitations ($n = 1$).