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ORIGINAL RESEARCH

Pregnancy and Progression of Cardiomyopathy in Women With LMNA Genotype-Positive

Anna I. Castrini (iD), MD; Eystein Skjølsvik, MD, PhD; Mette E. Estensen, MD, PhD; Vibeke M. Almaas (iD), MD, PhD; Helge Skulstad (iD), MD, PhD; Erik Lyseggen, MD, PhD; Thor Edvardsen (iD), MD, PhD; Øyvind H. Lie (iD), MD, PhD; Kermshlise C. I. Picard, MPH; Neal K. Lakdawala (iD), MD; Kristina H. Haugaa (iD), MD, PhD

BACKGROUND: We aimed to assess the association between number of pregnancies and long-term progression of cardiac dysfunction, arrhythmias, and event-free survival in women with pathogenic or likely pathogenic variants of gene encoding for Lamin A/C proteins (LMNA+).

METHODS AND RESULTS: We retrospectively included consecutive women with LMNA+ and recorded pregnancy data. We collected echocardiographic data, occurrence of atrial fibrillation, atrioventricular block, sustained ventricular arrhythmias, and implantation of cardiac electronic devices (implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator). We analyzed retrospectively complications during pregnancy and the peripartum period.

We included 89 women with LMNA+ (28% probands, age 41±16 years), of which 60 had experienced pregnancy. Follow-up time was 5 [interquartile range, 3–9] years. We analyzed 452 repeated echocardiographic examinations. Number of pregnancies was not associated with increased long-term risk of atrial fibrillation, atrioventricular block, sustained ventricular arrhythmias, or implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator implantation. Women with previous pregnancy and nulliparous women had a similar annual deterioration of left ventricular ejection fraction (−0.5/year versus −0.3/year, P=0.37) and similar increase of left ventricular end-diastolic diameter (0.1/year versus 0.2/year, P=0.09). Number of pregnancies did not decrease survival free from death, left ventricular assist device, or need for cardiac transplantation. Arrhythmias occurred during 9% of pregnancies. No increase in maternal and fetal complications was observed.

CONCLUSIONS: In our cohort of women with LMNA+, pregnancy did not seem associated with long-term adverse disease progression or event-free survival. Likewise, women with LMNA+ generally well-tolerated pregnancy, with a small proportion of patients experiencing arrhythmias.

Key Words: arrhythmias ■ cardiomyopathy ■ Lamin A/C ■ LMNA ■ outcome ■ pregnancy

V ariants in gene encoding for Lamin A/C proteins (LMNA), are an important genetic cause of dilated cardiomyopathy (DCM).[1] In familial DCM, LMNA variants are found in 4% to 8% of the cases,[2] and in up to 33% in DCM with concomitant electrical conduction disease.[3] The penetrance of LMNA variants is age-dependent and approaches 100% by middle age with variable clinical expression, including early onset of atrioventricular block, atrial fibrillation (AF), and DCM.[4] The disease course is malignant with high rates of ventricular arrhythmias (VA) and sudden cardiac death, stroke, and progression to end stage heart

CLINICAL PERSPECTIVE

What Is New?

- In women with LMNA+, number of previous pregnancies was not associated with long-term worsening of electrical disease and occurrence of sustained ventricular arrhythmias, and did not accelerate cardiac dilatation.
- Number of deaths, left ventricular assistance device implantations, and heart transplantations did not differ significantly between nulliparous women and women with previous pregnancy in our cohort.
- Pregnancy was mostly well tolerated with a low number of maternal and fetal complications, but risk of arrhythmias during pregnancy cannot be excluded.

What Are the Clinical Implications?

- Women with LMNA+, without overt electric/structural cardiomyopathy, should not be suggested to refrain pregnancy.
- Pre-pregnancy counseling in high experience cardiomyopathy centers, to assess disease status and pregnancy-related risks, should be considered in these patients.
- During pregnancy, because of lack of systematic data on triggering of arrhythmic events, it can be reasonable to use ambulatory ECG monitoring in women with known LMNA+, independently of current phenotype.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
HTx	heart transplantation
LMNA	gene encoding for Lamin A/C proteins
LMNA+	pathogenic or likely pathogenic variants of LMNA
VA	ventricular arrhythmias

failure, with frequent need of left ventricular assistance device (LVAD) and heart transplantation (HTx).[5]

Recent reports have suggested a negative effect of both competitive[6] and non-competitive[7] sport on prognosis of patients with LMNA variants. Pregnancy can be regarded as a comparable state of prolonged exercise because of the hemodynamic stress related to increase in circulating blood volume, rise in stroke volume and heart rate, in addition to sympathetic stimulation and hormonal changes.[8,9] Thus, pregnancy might be associated with increased cardiac complications and number of pregnancies might affect long-term disease progression in LMNA cardiomyopathy. Cardiac disease in these patients often develops in early adulthood, but the tolerance and effect of pregnancy on disease progression have not been explored, with only few case reports available.[10] We aimed to investigate the association between pregnancy and long-term progression of cardiac dysfunction, arrhythmias and, survival outcomes in women with pathogenic or likely pathogenic variant of LMNA (LMNA+). Furthermore, we wanted to explore fetal and maternal adverse events, during pregnancy and peripartum period.

METHODS

Data Availability

The authors do not have the authority to share the data reported in the present article, because of the sensitive nature of the data collected for this study. The Approval of the Regional Committee for Medical Research Ethics limits sharing data with researchers inside or outside Norway for purposes of reproducing the results or replicating the procedures. The data can be made available to any additional research after formal application to the Regional Committee for Medical Research Ethics and explicit consent given from every study subject.

Independent Data Access and Analysis

Authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Study Population

We conducted a multicenter, retrospective, longitudinal study and included consecutive women with LMNA+ from the Unit for Genetic Cardiac diseases, Oslo University Hospital, Rikshospitalet, Norway, and from the cardiovascular genetics program of Brigham and Women's Hospital, Boston, USA. LMNA variants were classified locally (Oslo/Boston), in conjunction with reference laboratories and in keeping with consensus.[11] Only patients with pathogenic or likely pathogenic LMNA variants were included. We defined proband as the first individual in a family, without known history of LMNA+ related disease, who sought medical attention attributable to clinical manifestation of disease and underwent genetic testing. We defined baseline as time of first available echocardiographic examination, and last follow-up as last available echocardiographic examination before October 2019 or before implantation of LVAD or HTx. We recorded symptoms of heart failure at each visit and reported as New York Heart Association functional class. We collected medical history, including the number of previous pregnancies/births and spontaneous abortions

from medical records. Pregnancy ended with birth of a viable or death fetus were included in our analysis, and women with LMNA+ who experienced pregnancy with these characteristics were defined *women with previous pregnancy*. We defined *nulliparous* women with LMNA+ who never carried a pregnancy to birth of a viable or death fetus. Spontaneous abortions were not included in the total number of pregnancies. We recorded heart failure and anti-arrhythmic medical therapy. We additionally contacted patients by telephone to collect specific pregnancy-related information, including age at pregnancies, awareness of being LMNA+ at time of pregnancy, presence of symptoms before/during pregnancy, and use of medications before/during pregnancy. We recorded type of delivery and obstetric complications. In addition, we reported a detailed description on the subgroup of women with LMNA+ followed during pregnancy and peripartum period at our hospitals.

All patients from Oslo gave inform consent. Brigham and Women's Hospital waived consent for retrospective data. The study complied with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics.

Electrocardiography, Conduction Disease, and Arrhythmias

Arrhythmias were recorded during clinical visits from 12-lead resting ECG, exercise ECG, ambulatory ECG monitoring, and interrogation of implantable cardiac electronic devices. We obtained and analyzed 12-lead ECG in all participants at the time of echocardiographic examinations. All patients underwent at least one ECG Holter and exercise ECG. We recorded atrioventricular block I–III, AF and VA. Sustained VA was defined as aborted cardiac arrest or ventricular tachycardia with a frequency ≥120/min lasting >30 seconds or appropriate implantable cardioverter defibrillator (ICD) therapy.[5]

Echocardiography

All completed transthoracic echocardiographic examinations between inclusion and last clinical follow-up were analyzed. We excluded echocardiographic exams performed after LVAD implantation and/or HTx, and examinations done during infusion of cardiac inotropes. Data about left ventricular (LV) end-diastolic diameter and LV ejection fraction (EF) were collected.[12] We considered LV ejection fraction (EF)≤45% as threshold for significant LV systolic dysfunction.[13] A subset of patients were investigated with LV strain. LV global longitudinal strain was derived from speckle tracking analyses on 2D gray scale image loops with >50 frames per second from the 3 apical views and expressed as the average peak negative strain in a

16 segment LV model.[14] All measurements were performed masked to clinical outcome.

Statistical Analysis

We performed statistical analyses using Stata SE 16.1 (StataCorp LLC, Texas, USA). Values were expressed as mean with standard deviations, median with interquartile range (IQR), and frequencies with percentages. At last follow-up continuous variables were compared by unpaired Student *t*-test, Kruskal–Wallis test, or by ANOVA *F* test with Bonferroni correction, when more than 2 groups were compared. Categorical variables were compared by Fisher exact test. The composite of all-cause mortality, LVAD implantation, or HTx constituted the primary outcome (death/LVAD/HTx). To assess the effect of pregnancies, we divided the study population in subgroups according to the number of pregnancies and we compared nulliparous women and women with previous pregnancy at last follow-up.

We used a generalized estimating equation with individual level random effects, binomial family, and independent working correlation within our data. We recorded longitudinal nested data to increase the statistical strength of our analysis within participant. We applied generalized estimating equation to assess the odds of impending AF, atrioventricular block, sustained VA, ICD, or cardiac resynchronization therapy (CRT) defibrillator implantation, EF ≤45%, and of primary outcome in up to 452 examinations (=100% of observations), or less if data were not available. We aimed to adjust our analyses for statistically and clinically relevant covariates, and to interpret the results in the context of relatively few events. Therefore, we have kept the following 4 covariates in our multivariate analyses; (1) pregnancy, as main dependent variable; (2) age at last follow-up as a statistically and clinically important confounder, in addition to (3) missense mutations, and (4) probands status. The 2 latter were not statistically significant parameters in univariate analyses but were considered clinically important for prognosis in Lamin disease.

Key echocardiographic parameters from all the examinations taken during the study period were entered into a linear mixed model regression analyses with random individual intercept and exchangeable covariance structure. LV structural and functional deterioration in nulliparous women and women with previous pregnancy was assessed by interaction term between the time varying covariates number of pregnancies and age at examination.

Kaplan–Meier curves were generated, and we performed log-rank test to compare cumulative hazard risk of AF, sustained VA, and primary outcome between nulliparous women and women with previous pregnancy. The results of survival analysis were adjusted with a Cox regression multivariable analysis exploring

time to AF, to sustained ventricular arrhythmias and to death/LVAD/HTx. We included EF at baseline (for the outcomes sustained VA and primary outcome) in combination with age at baseline, and probands status (for the outcome AF). These covariates were considered clinically important. We used proportional hazard test to check deviation from proportionality and results confirmed the fitness of our models.

P values were 2-sided, and values <0.05 were considered significant.

RESULTS

Clinical Characteristics

Eighty-nine women with LMNA+ (28% probands) were included (58 from Oslo University Hospital and 31 from Brigham and Women's Hospital), 24 (27%) of them with missense mutations. Age at baseline was age 41±16 years (Table 1). A list of included LMNA variants is provided on Table S1. Patients were followed from November 2001 to October 2019 with median follow-up time of 5 (IQR, 3–9) years, without differences between the pregnancy groups (Table 2). Most women with previous pregnancy, experienced pregnancy before clinical debut of cardiac symptoms or diagnosis of an LMNA variant. Clinical follow-up started in median 14 (IQR, 10–22) years after last pregnancy. The total time from first pregnancy to the last follow-up was median 22 (IQR, 17–32) years. We analyzed 452 available echocardiographic examinations, with a median of 4 (IQR, 2–8) examinations per patient.

At baseline, 19 (21%) patients had atrioventricular block, 39 (44%) AF, 10 (11%) patients had experienced sustained VA, and 10 (11%) had ICD/CRT-defibrillator (Table 1). Twenty-one (24%) patients were in New York Heart Association class II–IV, and 10% had history of stroke or transient ischemic attack. Most of patients had LV diameter and systolic function, by LV EF and global longitudinal strain, preserved at baseline, although 21% of patients had LV EF≤45 (Table 1).

At last follow-up, 29 (33%) women were nulliparous and 60 (67%) were women with previous pregnancy, including 13 (22%) with 1 pregnancy, 31 (51%) with 2 pregnancies, and 16 (27%) with ≥3 or more pregnancies (Table 2). Among nulliparous women, 23 (79%) were still in childbearing age (15–49 years) at last follow-up, and 13 (45%) women were aged ≤25 years.

Electrical, Structural Disease Progression, and Outcome in Patients Grouped by Pregnancy

At last follow-up, women with previous pregnancy were older then nulliparous and, as expected, age had a parallel increase with number of pregnancies (Table 2).

Table 1.   Clinical Characteristics and Imaging Parameters of 89 Women With LMNA+ at Baseline and Last Follow-Up

Clinical characteristics	Baseline (n=89)	Last follow-up (n=89)
Age at first pregnancy (y±SD)	…	27±5
Age (y±SD)	41±16	46±16
NYHA class II–IV (n, (%))	21 (24)	32 (36)
Atrioventricular block I–III (n, (%))	19 (21)	24 (27)
Atrioventricular block I	11 (12)	9 (10)
Atrioventricular block II	2 (2)	5 (6)
Atrioventricular block III	6 (7)	10 (11)
Atrial fibrillation (n, (%))	39 (44)	52 (58)
Sustained VA (n, (%))	10 (11)	22 (25)
Medications and device therapy		
Beta-blockers (n, (%))	22 (25)	48 (54)
ACE inhibitors/ARBs (n, (%))	15 (17)	31 (35)
MRAs (n, (%))	8 (9)	16 (18)
AAs (n, (%))	8 (9)	2 (2)
ICD/CRT-D (n, (%))	10 (11)	51 (57)
Echocardiographic		
LV EF, %	53±11	50±13
LV EF≤45% (n, (%))	19 (21)	17 (19)
LV EDD, mm	51±6	51±7
LV GLS, %	−18±4	−16±4

Data are presented as n (%) or means±SD. Prevalence of arrhythmias and of treatments (medical and device therapy) is reported. LV global longitudinal strain refers to a subgroup of 58 patients with available strain measurements. AAs indicates anti-arrhythmic medications (sotalol, amiodarone, verapamil, flecainide, and dronedarone); ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; LV EDD, left ventricular end-diastolic diameter; LV EF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; MRAs, mineralocorticoid-receptor antagonist; NYHA, New York Heart Association; TIA, transient ischemic attack; and VA, ventricular arrhythmias.

During follow-up, 5 patients developed atrioventricular block, 3 patients developed atrioventricular block II, and 4 atrioventricular block III (Table 1). Thirteen new cases of AF occurred. At last follow-up, in total atrioventricular block was present in 24 (27%) patients and AF in 52 (58%), with higher prevalence in women with previous pregnancy compared with nulliparous women (Table 2). However, number of pregnancies was not associated with atrioventricular block (OR, 1.63; 95% CI, 0.65–4.07; *P*=0.30), nor with AF (OR, 1.17; 95% CI, 0.68–2.03; *P*=0.56), when adjusted for age, proband status, and missense mutation (Table 3). There was no difference in the age at onset of AF in nulliparous women and women with previous pregnancy (log rank, *P*=0.73), and time to AF was not significantly different between the groups after adjustment for age and EF at baseline, and probands status (Figure 1). Twelve patients developed VA during follow-up with an incidence of 13% and VA prevalence was of 22 (25%) patients at

Table 2. Clinical Parameters and Outcomes of 89 Women With LMNA+ Grouped by Previous Pregnancies at Last Follow-Up

	0 previous pregnancy (n=29)	1 previous pregnancy (n=13)	2 previous pregnancies (n=31)	≥3 previous pregnancies (n=16)	P value	≥1 previous Pregnancies (n=60)	P value 0 vs ≥1 pregnancy
Clinical characteristics							
Age at last follow-up, y	33±17	44±9	53±9*	57±12*	<0.001	52±11	<0.001
Follow-up time, y	4 [2–7]	4 [3–8]	6 [3–10]	5 [4–12]	0.83	5 [3–10]	0.13
Proband status (n, (%))	5 (17)	3 (23)	9 (29)	8 (50)	0.16	20 (33)	0.20
Missense mutation (n, (%))	6 (21)	3 (23)	8 (26)	6 (38)	0.68	17 (28)	0.60
NYHA class II–IV (n, (%))	11 (38)	2 (15)	13 (42)	6 (38)	0.30	21 (35)	0.53
Atrioventricular block I–III (n, (%))	4 (14)	4 (31)	13 (42)	6 (38)	0.004	23 (38)	<0.001
Atrial fibrillation (n, (%))	9 (31)	6 (46)	25 (81)	12 (75)	0.001	43 (72)	0.001
Sustained VA (n, (%))	4 (14)	3 (23)	9 (29)	6 (38)	0.36	18 (30)	0.11
Echocardiographic examination							
LV EF, %	53±14	53±12	48±13	45±12	0.25	48±12	0.18
LV EF≤45% (n, (%))	2 (7)	3 (23)	6 (19)	6 (38)	0.11	15 (25)	0.08
Delta EF (%)	−3±11	−7±8	−3±8	−4±10	0.82	−4±10	0.73
LV GLS, %	−16±4	−16±5	−15±4	−16±3	0.68	−15±4	0.42
LV End-diastolic diameter, mm	50±7	50±4	53±7	50±6	0.34	51±6	0.31
Medications and device therapy							
Beta-blockers (n, (%))	12 (41)	7 (54)	19 (61)	10 (63)	0.56	36 (60)	0.12
ACE inhibitors/ARBs (n, (%))	5 (17)	3 (23)	15 (48)	8 (50)	0.04	26 (43)	0.02
MRAs (n, (%))	3 (10)	0 (0)	7 (23)	6 (38)	0.04	13 (22)	0.17
AAs (n, (%))	0 (0)	0 (0)	2 (6)	0 (0)	0.63	2 (3)	1.00
ICD/CRT-D (n, (%))	9 (31)	7 (54)	25 (80)	10 (63)	0.003	44 (73)	0.001
Outcomes							
Death (n, (%))	2 (7)	1 (8)	3 (10)	2 (13)	0.95	6 (10)	0.52
Heart transplantation (n, (%))	4 (14)	1 (8)	3 (10)	4 (25)	0.50	8 (13)	0.57
LVAD (n, (%))	1 (3)	0 (0)	1 (3)	1 (6)	1.00	2 (2)	0.69
Death/LVAD/HTx, (n, (%))	6 (21)	2 (15)	5 (16)	6 (38)	0.39	13 (22)	0.56

Data are presented as n (%), means±SD or median [interquartile range]. Prevalence of arrhythmias, treatments (medical and device therapy), and outcome is reported. P value from ANOVA F-test with Bonferroni correction, Fisher exact test, and Kruskal–Wallis test. AAs indicates anti-arrhythmic medications (sotalol, amiodarone, verapamil, flecainide and dronedarone); ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CRT-D, cardiac resynchronization therapy defibrillator; Delta EF, difference between ejection fraction baseline and ejection fraction last follow-up; HTx, heart transplantation; ICD, implantable cardioverter-defibrillator; LVAD, Left ventricular assistance device; LV EDD, left ventricular end-diastolic diameter; LV EF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; MRAs, mineralocorticoid-receptor antagonist; NYHA, New York heart association; TIA, transient ischemic attack; and VA, ventricular arrhythmias.

*Post hoc P<0.05 versus 0 pregnancy

last follow-up, with similar rates in nulliparous women and women with previous pregnancy (Table 2), and with no effect of number of pregnancies (Table 3). Age at onset of sustained VA was similar between the 2 groups (log rank P=0.87), and time to VA was not significantly different between the groups after adjustments for EF at baseline (Figure 1).

LV systolic function was mildly impaired at last follow-up (Table 1) along with normal LV end-diastolic diameter. We found no difference in echocardiographic parameters between pregnancy groups (Table 2). Pregnancy did not increase the odds for LV EF ≤45% (Table 3). Nulliparous women and women with previous pregnancy had similar annual progression of

Table 3. Multivariable Analysis of Repeated Observations in 89 Women With LMNA+ Assessing Predictive Effects of Known Prognostic Factors and Number of Previous Pregnancies

Primary outcome and markers of disease progression	Prognostic factors	Odds ratio	95% CI	P value
Death/LVAD/HTx, n=452 (100%)	Age, y	1.05	0.99–1.11	0.09
	Pregnancy	0.67	0.35–1.30	0.24
	Proband status	13.7	3.67–50.8	<0.01
	Missense mutation	1.00	0.25–4.1	0.96
Atrioventricular block, n=279 (62%)	Age, y	1.05	0.98–1.11	0.16
	Pregnancy	1.63	0.65–4.07	0.30
	Proband status	13.5	0.93–195.4	0.05
	Missense mutation	0.61	0.14–2.69	0.51
Atrial fibrillation, n=447 (98%)	Age, y	1.06	1.02–1.11	<0.01
	Pregnancy	1.17	0.68–2.03	0.56
	Proband status	7.59	1.55–37.5	0.01
	Missense mutation	0.56	0.16–1.92	0.36
ICD/CRT-D, n=434 (96%)	Age, y	1.09	1.04–1.15	<0.01
	Pregnancy	0.70	0.36–1.38	0.31
	Proband status	11.2	2.13–58.8	<0.01
	Missense mutation	0.48	0.14–1.69	0.26
Sustained VA, n=447 (98%)	Age, y	1.02	0.98–1.06	0.32
	Pregnancy	1.13	0.68–1.86	0.64
	Proband status	2.25	0.77–6.57	0.14
	Missense mutation	1.30	0.44–3.84	0.63
LV EF≤ 45%, n=452 (100%)	Age, y	1.06	1.02–1.11	<0.01
	Pregnancy	1.04	0.66–1.63	0.88
	Proband status	7.17	2.26–22.8	<0.01
	Missense mutation	1.00	0.28–3.52	0.99

Generalized estimating equation with repeated observations; n=number of examinations (percent) with available data. Random effects by individuals, logit link, binomial family, and independent covariance structure. CRT-D indicates cardiac resynchronization therapy defibrillator; HTx, heart transplantation; ICD, implantable cardioverter-defibrillator; LV EF, left ventricular ejection fraction; LVAD, Left ventricular assistance device; n, number of examinations (percent) with available data; and VA, ventricular arrhythmias.

structural and functional LV disease, measured by LV EF, end-diastolic diameter, and global longitudinal strain (Table 4).

Women with previous pregnancy had higher prevalence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers medication, mineralocorticoid-receptor antagonist, and ICD/CRT-defibrillator device therapy (Table 2), while these differences were not present in age-adjusted analyses.

The primary outcome death/LVAD/HTx occurred in 19 (21%) patients, without differences across pregnancy groups. Number of pregnancies did not increase the odds for the primary outcome (OR, 0.67; 95% CI, 0.35–1.30; P=0.24). There was no difference in the age at occurrence of the primary outcome between nulliparous women and women with previous pregnancy (log rank 0.17), and time to primary outcome was not different between the groups after adjustments for EF at baseline (Figure 1).

Pregnancy and Peripartum Outcomes

Among the 60 women with previous pregnancies, mean age at first pregnancy was 27±5 years. A total of 125 pregnancies were reported, and we had available details of pregnancy and peripartum outcomes in 109 (87%) of them. Most of the women reported well-tolerated pregnancies and uncomplicated deliveries. Palpitations, dyspnea, and syncope were reported in 9 (8%), in 4 (4%), and in 3 (3%) pregnancies, respectively. Arrhythmias were detected in 9 (9%) pregnancies (Table 5). Two (2%) patients experienced sustained VA and anti-arrhythmic therapy was started or modified, and 1 patient received an ICD during pregnancy. Four patients were on medications before pregnancy, and 5 (5%) were on anti-arrhythmic medications during pregnancy (Table 5).

Vaginal delivery was predominant (Table 5). Because of obstetric reasons, 14% of women had caesarean sections, none for cardiac reasons. In total, 4 spontaneous abortions occurred in the early second trimester, but
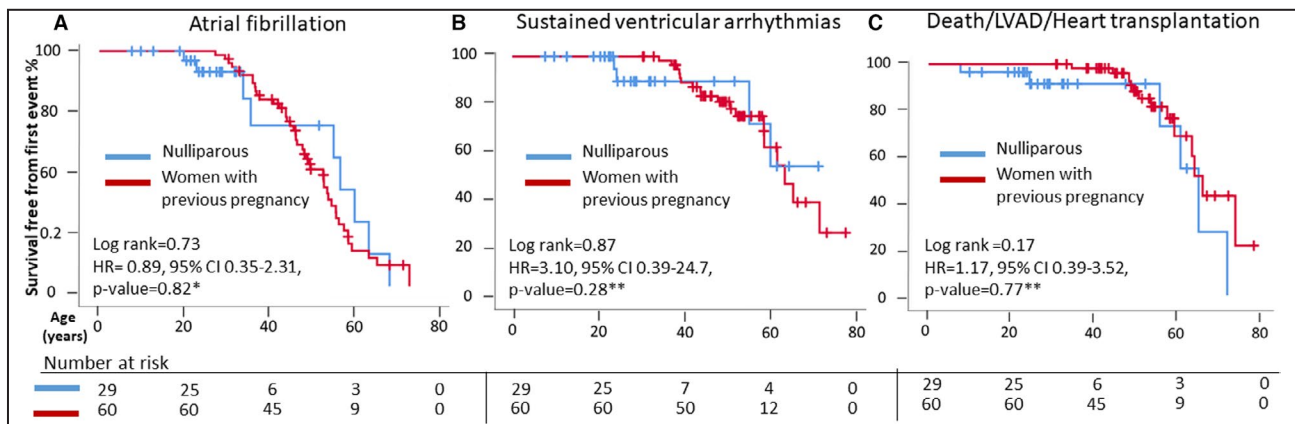
Figure 1. Survival free from arrhythmias and primary outcome.
Survival free from incident atrial fibrillation (**A**), sustained ventricular arrhythmias (**B**) and death, need for left ventricular assistance device or heart transplantation (**C**) did not differ between women with previous pregnancy (red line) and nulliparous (blue line) women. HR indicates hazard ratio from Cox models regression, exploring time to atrial fibrillation, sustained ventricular arrhythmias, and death/left ventricular assistance device/heart transplantation; and LVAD, left ventricular assistance device. *Adjusted for pregnancy, age, and ejection fraction at baseline, and probands status. **Adjusted for pregnancy and ejection fraction at baseline.

Table 4. Annual Structural Progression by Repeated Echocardiographic Assessments in Women With LMNA+ Grouped by Previous Pregnancy

	At baseline (n=89)	Progression rate 1 year (SE)	Last follow-up (n=89)	P value
LV EF (%), n=415 (92%)	53±11	−0.4 (0.0)	50±13	<0.001
Nulliparous	55±13	−0.3 (0.1)	53±14	0.003
Women with previous pregnancy	53±10	−0.5 (0.1)	49±12	<0.001
P for interaction		0.37		
LV EDD (mm), n=416 (92%)	50±6	0.1 (0.0)	51±6	<0.001
Nulliparous	49±7	0.2 (0.1)	50±7	<0.001
Women with previous pregnancy	51±6	0.1 (0.0)	51±6	0.02
P for interaction		0.09		
LV GLS (%), n=230 (51%)	−17±4	0.1 (0.0)	−16±6	0.03
Nulliparous	−17±5	0.0 (0.1)	−16±4	0.53
Women with previous pregnancy	−17±3	0.1 (0.0)	−15±4	0.01
P for interaction		0.35		

Values at baseline and last follow-up are presented as mean±SD; n=number of examinations (percent) with available data. Yearly progression rate with standard errors, P value for progression and interaction are calculated by linear mixed model statistics with exchangeable covariance structure and random individual intercept. LV EDD indicates left ventricular end-diastolic diameter; LV EF, left ventricular ejection fraction; and LV GLS, left ventricular global longitudinal strain.

without associated cardiac symptoms/complications. All women who experienced spontaneous abortion reported previous or subsequent successful births with uncomplicated pregnancies. No arrhythmic events or heart failure were described during peripartum period.

Three stillbirths were reported, none attributable to cardiac cases (1 umbilical cord strangulation, 1 of unknown etiology in a twin pregnancy, and 1 of unknown etiology in a single pregnancy through in vitro fertilization with sperm donation). None of these 3 women were aware of LMNA+ diagnosis, nor received cardiac medical therapy at the time of stillbirth, and all reported prior or subsequent uncomplicated pregnancy.

Patients With LMNA+ Prospectively Followed During Pregnancy and Peripartum Period

Of all 89 patients, we prospectively followed 6 women with LMNA+ (aged 31±3 years) during pregnancy and peripartum period at our hospitals (5 in Oslo, 1 in Boston). Four patients were probands, and 1 of them

Table 5. Maternal Clinical Characteristics During Pregnancy and Peripartum Period and Obstetric and Fetal Outcomes

Maternal adverse cardiac event	(n=109)
Maternal mortality	0 (0)
Heart failure	0 (0)
Atrial fibrillation	2 (2)
PVCs	3 (3)
nsVA	2 (2)
Sustained VA	2 (2)
Thrombo-embolic complications	0 (0)
AAs	5 (5)
Symptoms	
Palpitations	9 (8)
Dyspnea	4 (4)
Syncope	3 (3)
Adverse obstetric outcomes	
Vaginal deliveries	94 (86)
Caesarean section	15 (14)
Emergency CS for cardiac reason	0 (0)
Pre-eclampsia	2 (2)
Spontaneous abortions >12 wk	4 (4)
Bleeding	1 (1)
Adverse fetal outcomes	
Fetal or neonatal death<1 wk	3 (3)
Low birth weight (<2500 g)	2 (2)
Preterm birth (<37 wk)	6 (6

Data are presented as *n* (%). Data on AF, nsVA and sustain VA refers to incident arrhythmias. AAs indicates anti-arrhythmic therapy (Metoprolol, Bisoprolol, Sotalol); CS, Caesarean section; nsVA, non-sustained ventricular arrhythmias; PVCs, premature ventricular contractions; and VA, ventricular arrhythmias.

was diagnosed with LMNA+ attributable to symptoms occurring during pregnancy.

Patients #1 and #2, with unknown genetic status, were referred because of palpitations during pregnancy. Sustained VA was detected in both cases. Patient #1, with a previous asymptomatic pregnancy, was effectively treated with Sotalol. She had spontaneous pre-term birth at week 31, without maternal complications. Patient #2 had syncope while on beta-blocker and was implanted with ICD during her second trimester. She had an uncomplicated delivery. Patient #3, proband and with 3 previous asymptomatic pregnancies, had palpitations attributable to premature ventricular complexes during her second pregnancy. She was efficiently treated with beta-blocker without further complications. Patient #4, proband, developed non-sustained VA during pregnancy, effectively treated with beta-blockers without further complication. Patients #5 and #6 were referred because of proband status and were free of cardiac symptoms. Both experienced uncomplicated pregnancies and deliveries.

All patients underwent at least 1 echocardiographic examination during pregnancy and all had normal LV end-diastolic diameter and LV EF.

DISCUSSION

To our knowledge, this is the largest study exploring the association between previous pregnancies, long-term development of cardiomyopathy, and outcomes in patients with LMNA+. Number of pregnancies was not associated with long-term worsening of electrical disease and occurrence of sustained VA and was not associated with worse primary outcome. Furthermore, pregnancy did not accelerate the progression of cardiac dysfunction in our cohort. The majority of women retrospectively reported uncomplicated pregnancies without increase in serious obstetric or fetal adverse events. A few selected patients followed during pregnancy experienced increased arrhythmic symptoms.

Effect of Pregnancy on Progression of Electrical Disease

The prevalence of AF and atrioventricular block was higher in women with previous pregnancy and increased with number of pregnancies. However, LMNA disease is strongly age-related and there was no association between number of pregnancies and AF or atrioventricular block when adjusted for age. Likewise, pregnancy did not affect prevalence of sustained VA, nor age at onset VA. We interpret these results as reassuring for long-term outcome in women with LMNA+. Our results support that pregnancy in LMNA+ is not comparable with exercise on arrhythmic risk. These results are similar to reports in arrhythmogenic cardiomyopathy with no effect of pregnancy on arrhythmic outcome.[15,16]

In our cohort, ICD/CRT-defibrillator implantation was higher in mothers, but not when adjusted for age. In our centers, we implant ICD/CRT when the pacemaker indication is fulfilled because of atrioventricular block, as recommended,[17] and this explains the high number of these devices in our study population. Overall, our finding suggested that 1 or several pregnancies in patients with LMNA+ did not accelerate electrical disease.

Effect of Pregnancy on Development of DCM

At the last follow-up, reduced LV function reflected the development of cardiomyopathy in our cohort, but reduced LV function did not relate to pregnancy or to numbers of pregnancies. Pregnancy was not associated with worse long-term progression of the structural

heart disease. This is in contrast to reports on harmful effects of physical exercise in LMNA+.[7] Possible explanations for this difference are hemodynamic adaptive mechanisms occurring in pregnancy, including systemic reduction in vascular resistance,[18] in contrast with prevalent increase in systemic resistance related to physical exercise.[19] Previous case reports showed no change in cardiac function in patients with LMNA+ during and after pregnancy.[10] Our study supports these case reports by a larger multi-center study.

Other studies reported data about pregnancy in women with overt DCM, without information on genotype.[20,21] Our patients were mostly pregnant in a pre-symptomatic phase, or during the "electrical phase" of LMNA cardiomyopathy, which may explain the non-eventful pregnancy reported in our cohort.

Effect of Pregnancy on Primary Outcome

A high proportion of patients died, received LVAD, or were heart transplanted in our cohort, in line with previous results.[5] Pregnancy did not increase odds for the primary outcome death/LVAD/HTx, which is reassuring for women with LMNA+ in childbearing age. Most of the patients in our cohort experienced pregnancy before LMNA+ genetic diagnosis and underwent the last follow-up years after last pregnancy. Furthermore, the total time from first pregnancy to last follow-up was median 22 years. Therefore, we believe to have covered a reasonable long-term follow-up.

Pregnancy Tolerance

It is well known that arrhythmic symptoms can increase during pregnancy.[22] In our small cohort of 6 patients followed prospectively, arrhythmias increased/occurred in 4 patients, and 2 of them had first time symptoms and sustained VA during pregnancy. Although a small and selected group, a tendency to triggered arrhythmias during pregnancy cannot be excluded.

In our population, pregnancy and delivery mostly occurred at a pre-symptomatic age. However, pregnancy in older women with LMNA+ with more advanced disease may be less tolerated.

Maternal and fetal complications were low, in line with results of previous case reports.[10] We reported 3 stillbirths, which is a higher number compared with the general population. However, we found no evident causative relationship with LMNA cardiomyopathy as described above.

Limitations

This was a retrospective cohort study with inherent limitations. The multicenter design allowed a higher number of included patients, but it could have introduced variability related to different clinical practice. Obstetric and fetal outcomes were mostly self-reported, which may lead to report- and recall bias, especially in patients who experienced pregnancy many years before the start of clinical follow-up. Most patients were in a relatively early phase of the disease when pregnant, so our population was therefore relatively healthy at time of pregnancy. Most nulliparous women in our cohort were young women and most of them still in childbearing age at last follow-up. Nevertheless, we cannot exclude that more seriously affected individuals, or individuals who have experienced a malignant family history, chose not to carry offspring, even if they were unaware of their genotype.

CONCLUSIONS

Pregnancies did not seem to be associated with worse electrical or structural cardiac disease, nor to worse event-free survival in women with LMNA+. Pregnancies and deliveries were globally well tolerated and uncomplicated, but a tendency of triggering arrhythmias during pregnancy could not be excluded in selected patients.

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SUPPLEMENTAL MATERIAL

Table S1: Pathogenic and likely pathogenic gene variants found in our cohort of LMNA+ women

Variant (HGVS)	Variant (protein)	Number of patients (%)	Type of mutation
c.43C>T	p.Q15X	2 (2)	Nonsense
c.73C>T	p.R25C	2 (2)	Missense
c.215G>T	p.R72L	1 (1)	Missense
c.234G>T	p.K78N	1 (1)	Missense
c.305T>C	p.L102P	1 (1)	Missense
c.427T>C	p.S143P	1 (1)	Missense
c.481G>A	p.E61K	1 (1)	Missense
c.585C>G	p.N195K	1 (1)	Missense
c.608A>G	p.E203G	4 (5)	Missense
c.629T>G	p.I210S	1 (1)	*not know
c.642delG	p.E214DfsX266a	6 (7)	Frameshift
c.673C>T	p.R225Ter	1 (1)	Nonsense
c.725C>T	p.A242V	1 (1)	*not know
c.863C>G	p.A288G	2 (2)	Missense
c.868G>A	p.E290K	1 (1)	Missense
c.886_887insA	p.R296QfsX35	16 (18)	Frameshift
c.961C>T	p.R321X	26 (29)	Nonsense
c.992G>A	p.R331Q	3 (3)	Missense
c.1003C>T	p.R335W	2 (2)	Missense
c.1129C>T	p.R377C	3 (3)	Missense
c.1189delC	p.Arg397Alafs*83	2 (2)	Frameshift
c.1146C>T	p.G382G	2 (2)	*not know
c.1215_1218delCTCA	p.Ser406Profs*73	1 (1)	Frameshift
c.1300_1307del	p.A434X	1 (1)	Nonsense
c.1541G>A	p.W514Ter	1 (1)	Nonsense
c.1609-1G>A	*not known	2 (2)	Splice site
c.1621C>T	p.R541C	1 (1)	Missense
c.(?_1)_(356_?)del	p.? (deletion exon 1)	2 (2)	*not know
c.?	p.? (deletion exons 10-12)	1 (1)	*not know

HGVS=Human Genome Variation Society