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CASE REPORT

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Cardiac Complications of Pregnancy in Desmoplakin Cardiomyopathy

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ABSTRACT

We present the course of 4 pregnancies in 3 women with desmoplakin cardiomyopathy, with a focus on changes in left ventricular ejection fraction and N-terminal pro-B-type natriuretic peptide levels from the prepregnancy period through the postpartum period, as well as maternal cardiac, obstetric, and neonatal outcomes. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;16:101880) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Pathogenic variants in the *DSP* gene, which encodes the desmosomal protein desmoplakin (DSP), are present in approximately 4% of adults who undergo genetic testing for dilated cardiomyopathy.[1] The phenotype of *DSP* cardiomyopathy is of predominant left ventricular (LV) involvement with episodic myocardial injury or inflammation, heart failure, and a heavy burden of ventricular arrhythmias.[2] Although the overlapping genetic etiology of peripartum and dilated cardiomyopathy was recently described, there are no descriptions of pregnancy outcomes in patients with pre-existing *DSP* cardiomyopathy. Studies in arrhythmogenic right ventricular cardiomyopathy have described a modest burden of ventricular tachycardia or heart failure (3 and 2 episodes, respectively, in 196 pregnancies).[3] In this study, we identified 3 patients who had a prenatal diagnosis of *DSP* cardiomyopathy by using the STORCC (Standardized Outcomes in Reproductive Cardiovascular Care) registry from 2011 to 2022,[4] and we report their prospectively observed 4 pregnancies (Table 1, Figure 1).

LEARNING OBJECTIVES

- To recognize potential risks associated with *DSP* cardiomyopathy in pregnant patients, including heart failure and ventricular tachyarrhythmias.
- To describe the clinical course of pregnancy for this group of patients.
- To emphasize the importance of a multidisciplinary cardio-obstetric approach to clinical care for patients with cardiomyopathy.

PATIENT 1: PREGNANCY 1

A 27-year-old gravida 1, para 0 woman underwent in vitro fertilization (IVF) during which preimplantation genetic testing was used to prevent transmission of the *DSP* variant. She had symptomatic premature ventricular contractions (PVCs) beginning 4 years before pregnancy that were treated with nadolol and radiofrequency ablation on 3 occasions. Prepregnancy

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ABBREVIATIONS AND ACRONYMS

DSP = desmoplakin

ICD = implantable cardioverter-defibrillator

IUGR = intrauterine growth restriction

IVF = in vitro fertilization

LV = left ventricular

LVEF = left ventricular ejection fraction

NICU = neonatal intensive care unit

NSVT = nonsustained ventricular tachycardia

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PVC = premature ventricular contraction

RV = right ventricular

SC = subcutaneous

evaluations included cardiac magnetic resonance imaging revealing an LV ejection fraction (LVEF) of 50% and nearly circumferential, epicardial late gadolinium enhancement involving the basal and middle left ventricle. Genetic testing revealed a heterozygous, likely pathogenic variant in *DSP* c.7563_7566del (p. Asp2521Glufs*39). A primary prevention subcutaneous (SC) implantable cardioverter-defibrillator (ICD) was implanted 2 years before pregnancy. A preconception echocardiogram revealed normal biventricular size, an LVEF of 50%, and mildly depressed right ventricular systolic function. Nadolol was continued during pregnancy for treatment of PVCs.

Throughout pregnancy, she experienced worsening palpitations, orthopnea, and intermittent effort intolerance. However, LVEF by echocardiography remained stable, she did not develop signs of congestion, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels remained within the normal range. She underwent induction of labor at 37.9 weeks for nonreassuring fetal testing results and was monitored on telemetry intrapartum without events. Delivery was complicated by a postpartum hemorrhage (estimated blood loss >1,000 mL) and neonatal hypoglycemia. She breastfed without complications.

Some improvement in dyspnea was noted during the postpartum period; however, palpitations increased, and Holter monitoring revealed nonsustained ventricular tachycardia (NSVT) and 2.4% PVCs.

PATIENT 1: PREGNANCY 2

The following year, the same woman presented with a spontaneous pregnancy. Her first trimester echocardiogram imaging was stable. She continued on nadolol, and metoprolol tartrate was taken as needed for increasing palpitations in the first trimester.

At 35 weeks' gestation, she developed orthopnea, paroxysmal nocturnal dyspnea, and increasing palpitations. She was hospitalized at 38 weeks after an echocardiogram revealed worsening systolic function (LVEF, 35%), and venous congestion was noted on examination. NT-proBNP levels were stable from first trimester levels at 251 pg/mL. She was treated with furosemide, and labor was induced at 38 weeks, with telemetry monitoring. She had an uncomplicated vaginal delivery of a healthy infant.

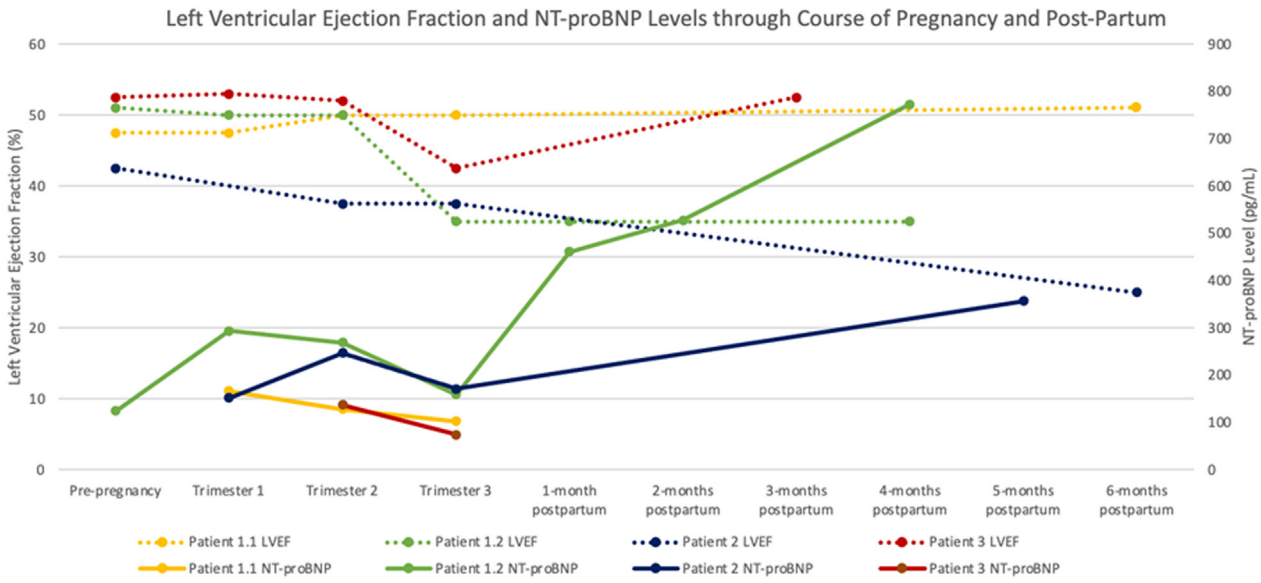
The patient required furosemide in the postpartum period for recurring dyspnea but had no further

TABLE 1 Individual Characteristics

	Patient 1.1	Patient 1.2	Patient 2	Patient 3
Age, y	27	29	32	32
Obstetric history	G1P0	G2P1	G2P1	G2P1
Type of pregnancy	IVF; singleton	Spontaneous; singleton	Spontaneous; singleton	IVF; monochorionic, diamniotic twin gestation
GA at delivery (weeks)	37.9	38	37.6	33.9
Type of delivery	Induced vaginal delivery	Induced vaginal delivery	Spontaneous vaginal delivery	Cesarean delivery
Cardiac monitoring at delivery	Telemetry	Telemetry	Telemetry	Telemetry
Cardiac history	Symptomatic PVCs		Cardiac arrest, PVCs, AVNRT	Cardiac arrest, PVCs
Previous cardiac interventions	PVC ablation (× 3); SC ICD implantation		SC ICD implantation, AVNRT ablation	SC ICD implantation
Cardiac outcomes	None	Decrease in LVEF in third trimester with symptomatic HF	Decrease in LVEF in second trimester without symptomatic HF	None
Obstetric outcomes	Postpartum hemorrhage	None	Chord plexus cyst, shortened cervix	Oligohydramnios, IUGR, preterm delivery
Neonatal outcomes	Hypoglycemia	None	Neonate with pathogenic *DSP* variant	SGA (<10%), NICU admission
Antepartum cardiac medications	Nadolol	Nadolol, metoprolol tartrate (as needed), furosemide (20 mg IV × 1) before labor	Metoprolol succinate, aspirin	Nadolol
Postpartum cardiac medications	Spironolactone, furosemide, metoprolol succinate, lisinopril	Metoprolol succinate, spironolactone, furosemide, lisinopril	Metoprolol succinate, aspirin	Nadolol

AVNRT = atrioventricular nodal re-entrant tachycardia; *DSP* = desmoplakin gene; G = gravida; GA = gestational age; HF = heart failure; IUGR = intrauterine growth restriction; IV = intravenously; IVF = in vitro fertilization; LVEF = left ventricular ejection fraction; NICU = neonatal intensive care unit; NVST = nonsustained ventricular tachycardia; P = para; PVCs = premature ventricular contractions; SGA = small for gestational age; SC ICD = subcutaneous implantable cardioverter-defibrillator.

FIGURE 1 **LVEF and NT-proBNP in Pregnancy and Post Partum**



Left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels throughout the course of each pregnancy and up to 6 months post partum.

congestion on examination. However, NT-proBNP levels rose, and systolic function remained impaired 2 and 4 months after delivery (Figure 1). The patient continued taking metoprolol and diuretic agents, including spironolactone and furosemide. She again chose to breastfeed, and angiotensin type II receptor blockers were held.

PATIENT 2

A 32-year-old gravida 2, para 1 woman presented in her first trimester after a spontaneous conception. Arrhythmia history included a previous cardiac arrest after which an SC ICD was placed, frequent PVCs, and atrioventricular nodal re-entrant tachycardia treated by ablation. Genetic testing before pregnancy revealed a heterozygous, likely pathogenic variant in *DSP* c.1751delA (p. Glu584fs*52). Continuing palpitations following ablation prompted implantation of a loop recorder, present during pregnancy. At baseline, the patient reported NYHA functional class II capacity. Metoprolol succinate and aspirin were continued throughout pregnancy.

An echocardiogram obtained 2.5 years before pregnancy revealed an LVEF of 40% and low-normal right ventricular (RV) systolic function. Repeat echocardiogram imaging obtained at 14 weeks' gestation revealed worsening systolic dysfunction (LVEF, 35%). Cardiopulmonary exercise testing performed at 16 weeks revealed a decline in functional capacity, with a peak oxygen consumption of 15 mg/kg/min (56% predicted), blunted systolic blood pressure response (90 and 96 mmHg at rest and peak exercise, respectively), and frequent multifocal PVCs. Given her poor functional capacity and high risk of progressive heart failure, she was advised to consider pregnancy termination; however, she elected to continue the pregnancy. She remained stable from a cardiovascular standpoint throughout the remainder of the pregnancy. Echocardiograms at 22 and 35 weeks' gestation revealed unchanged LVEFs. No additional cardiac medications were required during pregnancy. She was observed antenatally for a short cervix.

The patient had an uncomplicated spontaneous vaginal delivery at 37.6 weeks. She was monitored with telemetry throughout labor and for 12 hours post partum without events. The infant developed tachypnea resulting in neonatal intensive care unit (NICU) admission. Genetic testing revealed that the infant was positive for the *DSP* variant. There were no maternal postpartum complications following pregnancy, and the patient breastfed without concerns. At 18 months post partum, she was without

congestion or worsening symptoms, and an echocardiogram revealed an LVEF of 25%.

PATIENT 3

A 32-year-old gravida 2, para 1 woman underwent IVF with preimplantation genetic testing, resulting in a monochorionic, diamniotic twin pregnancy. The patient experienced a cardiac arrest 10 years earlier, for which an SC ICD was placed. Preconception cardiac evaluations included stress testing and echocardiography. Genetic testing performed 1 year before pregnancy revealed a heterozygous pathogenic variant in *DSP* c.2236del (p. Val746Tyrfs*19). Cardiac medications included nadolol, continued throughout pregnancy for symptomatic PVCs. An echocardiogram in the first trimester revealed an LVEF of 50% and normal RV size and function. NT-proBNP levels were within the normal range (137 pg/mL). ICD interrogation in the second trimester revealed rare NSVT. The patient remained clinically stable without sustained arrhythmias. In the third trimester, there was a modest decline in LVEF to 45%, although LVEF remained low normal and stable thereafter.

The pregnancy was complicated by intrauterine growth restriction (IUGR) of both twins and oligohydramnios during the third trimester. The patient was consequently admitted at 33.9 weeks' gestation for induction of labor. Vaginal delivery was planned with telemetry monitoring during active labor. However, nonreassuring fetal heart tracings after induction prompted urgent cesarean delivery. The patient tolerated the procedure well, and telemetry was continued for 6 hours after delivery. Both neonates were admitted to the NICU for prematurity.

The patient remained stable in the postpartum period. Her echocardiogram was unchanged. Nadolol dosage had been decreased (from 80 mg to 40 mg) during the third trimester in response to the finding of IUGR but was increased back to 80 mg post partum for recurrence of palpitations. There were no new arrhythmias or other cardiac complications. The patient successfully breastfed through the postpartum period.

DISCUSSION

Among 4 pregnancies in 3 patients with *DSP* cardiomyopathy, a decline in systolic function was observed in 2 pregnancies, symptoms of congestive heart failure accompanied by systolic functional decline occurred in 1 patient, and there were no cases of malignant arrhythmias. All patients received preconception counseling with a cardiologist and a maternal-fetal specialist, and the plan for cardiac monitoring and contingencies for worsening cardiac function were discussed. All 4 deliveries were well tolerated from a cardiac perspective, including the postpartum hemorrhage in 1 patient. Of note, vaginal deliveries were completed in 3 of the 4 pregnancies, and the 1 cesarean delivery was performed for noncardiac complications of induction, thus suggesting the safety of vaginal delivery in patients with cardiomyopathies. Findings from these 4 pregnancies suggest that there may be an increased risk of decline in systolic function during pregnancy among patients with *DSP* cardiomyopathy. These observations suggest that patients will need careful echocardiographic follow-up throughout pregnancy and in the postpartum period. It is important that patients with *DSP* cardiomyopathy who wish to become pregnant undergo prepregnancy counseling and are followed closely by a multidisciplinary cardio-obstetric team. Furthermore, the unique phenotype of and potentially increased risk for systolic decline during pregnancy in patients with *DSP* cardiomyopathy support the recommendation for genetic testing in patients with undiagnosed cardiomyopathies to tailor cardiac and obstetric care to these patients appropriately. Future studies of patients with *DSP* cardiomyopathy will be necessary to guide clinical recommendations for this group of patients.

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REFERENCES

1. Pugh TJ, Kelly MA, Gowrisankar S, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. *Genet Med*. 2014;16:601-608.

2. Smith ED, Lakdawala NK, Papoutsidakis N, et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2020;141:1872-1884.

3. Schaufelberger M. Cardiomyopathy and pregnancy. *Heart*. 2019;105:1543-1551.

4. Valente AM, Landzberg MJ, Gauvreau K, et al. Standardized outcomes in reproductive cardiovascular care: the STORCC initiative. *Am Heart J*. 2019;217:112-120.

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