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CONGENITAL HEART DISEASE

CASE REPORT: CLINICAL CASE

Twin Pregnancy in Patient With Fontan Circulation and Homozygous *MTHFR* Mutation

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ABSTRACT

Singleton pregnancy in Fontan patients is burdened by a significant maternal cardiovascular and obstetric risk. The cardiac workload in a twin pregnancy is greater and could place Fontan-palliated patients at an increased risk of complications. We report a case of a woman with Fontan circulation and homozygous *MTHFR* mutation who had a twin pregnancy. (JACC Case Rep. 2024;29:102526) © 2024 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/).

HISTORY OF PRESENTATION

A 35-year-old woman with Fontan circulation was followed by the adult congenital heart disease (ACHD) unit in a tertiary referral hospital. The patient became naturally pregnant for the third time and notified our ACHD team when she was at 9 weeks of gestation. At that time, her vital parameters revealed a regular heart rate at 102 beats/min, blood pressure of 129/85 mm Hg, and a stable oxygen saturation at 98%. On physical examination, her jugular venous pressure was not elevated, and no peripheral edema was observed. Echocardiography confirmed a preserved single-ventricle ejection fraction (EF) (Video 1) and mild mitral regurgitation (MR) (Video 2). The fetal scan showed a dichorionic diamniotic twin pregnancy.

LEARNING OBJECTIVES

- To establish a correct cardiovascular maternal risk stratification in Fontan patients before pregnancy.
- To perform a correct follow-up and multidisciplinary evaluation in Fontan patients during pregnancy.

PAST MEDICAL HISTORY

The patient was diagnosed with type IB tricuspid atresia and underwent the Fontan operation with an extracardiac conduit at 4 years of age. She had a regular follow-up, and preconception counseling was undertaken after a complete clinical assessment for risk stratification (modified World Health Organization [WHO] class III).

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ABBREVIATIONS AND ACRONYMS

ACHD = adult congenital heart disease

CS = cesarean section

EF = ejection fraction

MR = mitral regurgitation

PROM = premature rupture of membranes

WHO = World Health Organization

Two previous miscarriages occurred during the first trimester. Because of her miscarriage history, thrombophilia screening was performed, and homozygous *MTHFR* mutation was diagnosed.

DIFFERENTIAL DIAGNOSIS

Risk stratification in modified WHO class III or IV (maternal rate of cardiovascular events 19%-27% vs 40%-100%)[1] depends on clinical status, functional class, development of Fontan complications, atrioventricular valve regurgitation, and EF.

INVESTIGATIONS

A complete clinical assessment for risk stratification before pregnancy was performed. The patient was asymptomatic from a cardiovascular perspective (NYHA functional class I) and rest saturation (98%). A cardiopulmonary exercise test showed a normal blood pressure and heart rate response on exertion with a peak Vo_2 of 1,406 mL/min (18.5 mL/kg/min), which represented the 50th percentile if compared with patients with the same age and disease. No significant saturation decrease was observed during the test.

Her last magnetic resonance imaging study confirmed a normal single-ventricle EF (57%), mild MR (RF, 15%), and patent extracardiac conduit with no segmentary stenosis of the pulmonary arteries. A systemic-pulmonary collateral circulation (approximately 20% of the overall pulmonary venous return) and a venous connection between the azygos and the right inferior pulmonary vein were also observed. Blood tests showed normal renal and liver function with a brain natriuretic peptide of 27.8 pg/mL. α-Fetoprotein was negative, and liver ultrasound showed slightly heterogeneous parenchyma with no evident fibrosis or nodules.

MANAGEMENT

After a careful counseling and cardiovascular risk discussion, the patient decided to continue the pregnancy. The usual acetylsalicylic acid was suspended, and a daily prophylactic low-molecular-weight heparin injection was started. A joint cardiology and gynecology clinical follow-up was pursued monthly with blood tests, electrocardiograms, serial echocardiography, and fetal scans.

At 29 weeks of gestation, a reduction in her resting oxygen saturation was observed (from 98% to 92%), and oral furosemide 25 mg was started. No cardiovascular symptoms or major maternal complications occurred throughout the pregnancy. A multidisciplinary discussion was arranged when the patient was 30 weeks pregnant, and an elective caesarean section (CS) under epidural anesthesia was planned at 36 weeks of gestation.

Unfortunately, the patient presented with a premature rupture of membranes (PROM) with uterine contractions at 35 weeks, and an emergency CS was performed. The first twin was a boy with a birth weight of 1,430 g, defined as small for gestational age, and the second twin was a girl with a birth weight of 1,390 g, defined as small for gestational age. A neonatal echocardiography was performed in both twins, and the female twin's scan revealed a small interventricular septum defect with pulmonary valve stenosis. The postnatal course for both twins was regular, and they were discharged 15 and 30 days after delivery, respectively.

DISCUSSION

The number of patients with Fontan circulation who survive into adulthood and reach a childbearing age has increased over the past decades.[2-4] Pregnancy in this population was rarely described in the past; however, a large number of pregnant women with this surgical palliation have been reported.[5-7] The modified WHO classification of maternal cardiovascular risk during pregnancy allocate Fontan women in good status in class III[1]; nevertheless, this risk can change depending on several pathophysiological factors.

The most frequent complication in these patients is a premature delivery due to cardiovascular or obstetric reasons. Supraventricular arrhythmias and progressive single-ventricle dysfunction are the most frequent cardiac complications, whereas thromboembolic or hemorrhagic events are usually rare but a matter of concern.[5-7]

The hemodynamic changes during pregnancy are usually well tolerated in healthy women,[8] whereas an increasing cardiac output is strictly dependent on preload and systemic venous return in women with Fontan circulation.[7] The cardiac workload required in a twin pregnancy is greater than in a singleton pregnancy,[9] and the cardiovascular risk is potentially increased.

Twin pregnancies are very rare in patients with Fontan circulation, with only 3 cases reported in the literature.[10-12] Nir et al[10] described a twin pregnancy in a 21-year-old patient with Fontan circulation treated with clomiphene citrate by her gynecologist after a previous spontaneous miscarriage. Her cardiac

background was congenitally corrected transposition of the great arteries with large ventricular septal defect, right-sided mitral valve stenosis, and hypoplastic left ventricle and subpulmonary stenosis. She underwent Fontan palliation with a lateral tunnel at 3 years of age. The patient was referred to an ACHD team at 30 weeks of gestation when she complained of shortness of breath and showed a decline in exercise capacity (NYHA functional class II). On the echocardiogram, a good single-ventricle systolic function and mild to moderate atrioventricular valve regurgitation were observed. No arrhythmias occurred throughout the pregnancy. A CS was performed because of PROM at 33 weeks of gestational age. Fatigue persisted in the postpartum period.

In the second case, Nair et al[11] reported a pregnancy in a 29-year-old woman born with tricuspid atresia who underwent a late extracardiac Fontan completion at the age of 19 years. At the time of discharge, her cardiac function was reported as normal. After surgery, she was lost to follow-up. The patient presented with signs of heart failure (NYHA functional class III/IV), reduced EF (45%), and mild MR at 33 weeks of gestation (spontaneous pregnancy). An emergency CS was performed at 34 weeks of gestation because of a premature onset of labor. Postoperatively, a clinical deterioration occurred, and a further decrease in the single-ventricle systolic function (EF of 25%) with moderate MR were observed. She was medically treated with improvement in her single-ventricle systolic function (EF of 45%) and discharged as clinically stable 1 week after delivery.

In the third case, reported by Morita et al,[12] a twin pregnancy occurred in a 32-year-old Fontan-palliated woman inducted with clomiphene citrate. She was referred at 6 weeks of gestation, and the first echocardiography showed a single ventricle with left morphology (cardiac background of type II tricuspid atresia) with preserved EF and mild MR. She started to complain of shortness of breath since she was 26 weeks pregnant, and the echocardiography showed a worsened MR (first to second degree). Moreover, the pregnancy was complicated by complete placenta previa. An emergency CS was performed at 29 weeks because of massive genital bleeding. A postnatal echocardiography showed a reduced EF of the single ventricle (49%) and a third-degree MR. A postoperative cardiac catheterization demonstrated a leak between the lateral tunnel and the atrium, which was considered to be the cause of hypoxemia during peripartum.

In these 3 cases reported in literature, premature delivery occurred, and the 3 patients experienced a reduction in functional capacity. In 2 cases a decreased EF of the single ventricle was described. In our experience, our patient had a premature delivery because of PROM, but the pregnancy was well tolerated throughout, and no cardiovascular symptoms or major complications occurred. Our positive experience probably was because of the patient's underlying condition, which was different from those reported above.

Our patient underwent Fontan palliation at 6 years of age and had a regular follow-up during childhood and adulthood. When she expressed the desire to become pregnant, proper counseling was offered after a careful clinical assessment. Her resting saturation was 98%, and the echocardiogram confirmed a preserved systolic function of her left single ventricle with mild MR. She underwent a cardiopulmonary exercise test for cardiovascular risk stratification, and a second-level imaging was also performed as recommended.[3] As soon as the patient became spontaneously pregnant, she informed our team, and a monthly joint clinical follow-up with gynecologists was arranged. In addition, a thrombophilia screening was performed before pregnancy because of her history of miscarriage, and homozygous *MTHFR* mutation was diagnosed.[13,14] A correct anticoagulation therapy was provided to reduce thrombotic risk, and no thromboembolic complications occurred during pregnancy or in the puerperium.

FOLLOW-UP

Our patient was discharged 1 week after delivery, and prophylactic low-molecular-weight heparin injections were continued throughout the puerperium. Her postpartum period was free from cardiovascular maternal events. Vital parameters remained within the normal range with an oxygen saturation at 98%. A follow-up echocardiogram confirmed a preserved single-ventricle EF (Video 3), stable mild MR (Video 4), and normal flow in the Fontan pathway 6 weeks after delivery.

CONCLUSIONS

Patients with Fontan circulation have an increased risk of cardiovascular and obstetric complications from the time of conception. Adverse fetal events, such as premature delivery and low birth weight, may also occur. According to our experience, patients with Fontan palliation can face even a twin pregnancy if

the preconception cardiovascular status is favorable and if an expert and multidisciplinary follow-up is planned from the beginning of the first trimester.

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APPENDIX For supplemental videos, please see the online version of this paper.