NEONATAL HEMODYNAMICS Research Centre

Case Report

Severe hypertrophic obstructive cardiomyopathy in a term infant born to a diabetic mother

Authors: Dr. Floriane Brief, MD; Dr. Andréanne Villeneuve, MD, M.Sc, FRCP(c); Dr. Anie Lapointe MD, MSc, FRCP(c)
Affiliations: CHU Sainte Justine, University of Montreal, Division of Neonatology, Montreal, QC, Canada.

Background:
The case being presented is severe hypertrophic obstructive cardiomyopathy (HOCM) associated with poorly controlled maternal diabetes and complicated by a refractory shock state secondary to severe pulmonary hypertension.

Neonatal hypertrophic cardiomyopathy associated with maternal diabetes has a diverse range of neonatal presentations and outcomes[1]. This case underscores the necessity of maintaining a high degree of vigilance for severe HOCM, even with a recent normal fetal heart ultrasound, and emphasizes the importance of echocardiographic-guided therapeutic decisions in such patients.

Informed consent was obtained from the parents.

Key learning point:

- The third trimester fetal echocardiography in mothers with maternal diabetes does not predict the severity of the postnatal clinical presentation.
- Targeted neonatal echocardiography is much needed in the assessment of severe cases of HOCM complicated by severe pulmonary hypertension (PHT) and crucial to assess treatment response.
- Optimization of the severe PHT treatment and of the diastolic function were the cornerstone in the management of this case.

Clinical Presentation:
Prenatal and Birth History
The mother was multigravida (G4P2) and her current pregnancy was unremarkable except for poorly controlled Type 1 diabetes mellitus (HbA1C=13.5%). Fetal ultrasound revealed normal morphology, but fetal macrosomia was suspected in the second trimester. A fetal echocardiogram performed at 28 weeks of gestational age was reported as normal. Maternal serologies were all negative, and Group B Streptococcus was positive, with appropriate antibiotic prophylaxis administered.

A male infant was born at 37 weeks' gestation with a birth weight of 4700 g (>97th%) in a level 1 nursery hospital via an urgent Cesarean Section due to fetal decelerations and macrosomia. Apgar scores at 1, 5 and 10 minutes were 2, 5 and 6, respectively. Delivery room resuscitation involved 3 minutes of positive pressure ventilation and placement on continuous positive airway

pressure (CPAP) with 100% FiO_2. The infant was admitted to the nursery and given IV nutrition and antibiotics due to suspected neonatal infection.

An urgent echocardiography was performed by a local cardiologist at 30 minutes of life due to persistent hypoxemia. The study revealed significant left ventricular hypertrophy, suprasystemic pulmonary hypertension (PHT), and a large patent ductus arteriosus (PDA) with exclusive right-to-left shunting. Based on recommendations from a phone consultation with a neonatologist, endotracheal intubation was performed to secure the airway, milrinone was started at 0.3 mcg/kg/min, and the baby was transferred to a level 4 neonatal intensive care unit (NICU).

Medical History:
On the first day of life, the infant had severe and refractory PHT, requiring 100% oxygen despite being on high frequency ventilation (HFV) with a mean airway pressure (MAP) of 13cmH_2O, inhaled nitric oxide (iNO) at 20 ppm, and a milrinone infusion at 0.3 mcg/kg/min. An umbilical venous catheter was inserted. The chest radiograph revealed significant cardiomegaly, with a cardiothoracic ratio of 73% and relatively clear lungs (Figure 1).

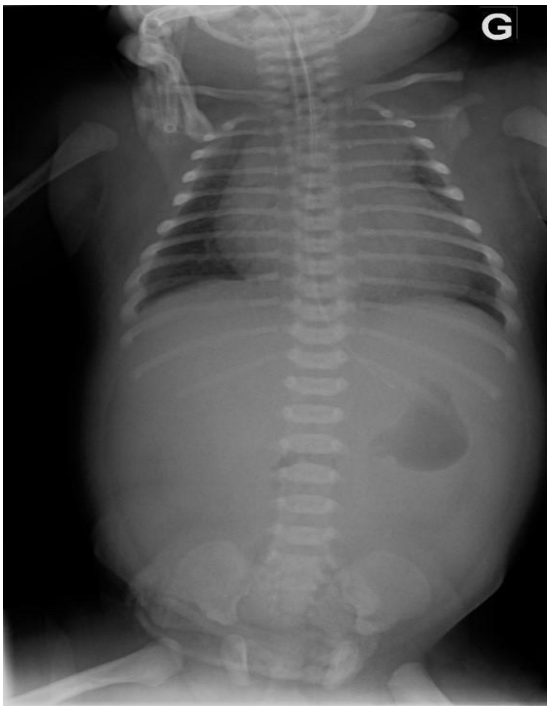


Figure 1: Chest and abdominal radiographs after admission to NICU

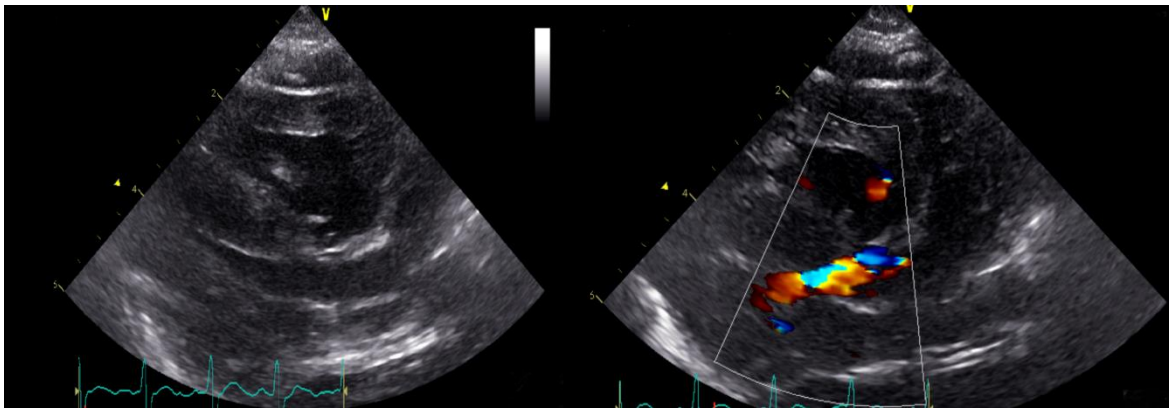
At 8 hours of life, a norepinephrine (NE) infusion was added at 0.5 mcg/kg/min following 2 boluses of normal saline to support blood pressure. An echocardiogram was repeated at 12 hours of life, revealing severe PHT with a septal curve type 3, right-to-left shunting via a large PDA, and severe interventricular septum (IVS) hypertrophy (*Z-score* of 5.1). The FiO_2 remained high, but gradually decreased to 50% at 28 hours of life. At 40 hours of life, arterial blood pressure was 53/31(38) mmHg, while the difference between pre and post ductal saturations increased to 10%. Concurrently, the FiO_2 requirement increased from 50 to 70%.

Hemodynamics consultation

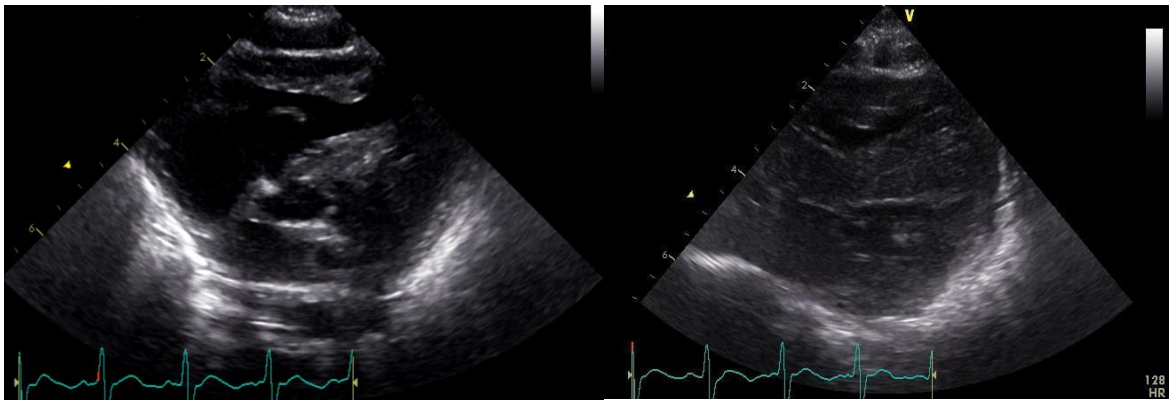
A hemodynamic consultation was requested at 43 hours of life. At the time of the targeted neonatal echocardiography (TnECHO) the patient was on HFO ventilation (mean airway pressure of 13 mmHg, amplitude 35), FiO_2 at 50% and iNO at 20 ppm. The blood pressure was 44/30mmHg (mean blood pressure (MBP) of 35mmHg), the blood gas showed pH= 7.24, pCO2= 48 mmHg, $HCO3^-$= 20 mmol/L, lactate=7.4 mmol/L and urine output was normal. The cardiovascular treatment in place included NE at 0.08 mcg/kg/min, milrinone at 0.3 mcg/kg/min and iNO at 20 ppm.

The TnECHO revealed: severe biventricular hypertrophy (Figure 2.1 and 2.2) (*Z-score 7.5SD*) with impaired left ventricular output (Figure 2.1), a small and restrictive PDA (Figure 2.3), supra systemic PHT with a septal curve type 3 in systole and diastole (Figure 2.2), pulmonary pressures were estimated at 60 mmHg according to the tricuspid regurgitation jet. Both ventricles exhibited severe hypertrophy and impaired diastolic function (mitral E/A= 0.64) and impaired tricuspid annular plane systolic excursion (TAPSE) (6.2 mm, *Z-score -2SD*). Left ventricular output (LVO) was decreased (130 cc/kg/min) but right ventricular output (RVO) was normal (222 cc/kg/min).

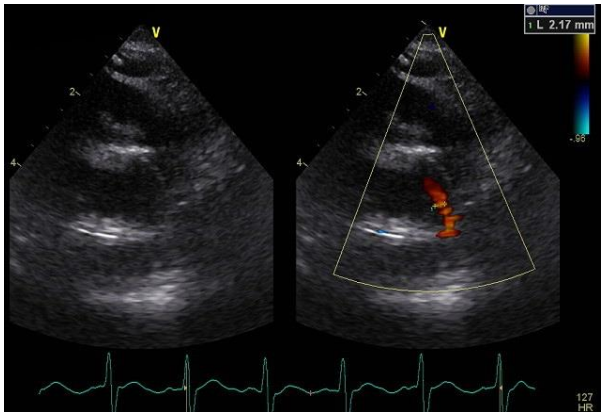
Figure 2: TnECHO images at 43 hours of life



2.1 Long axis view
Severe hypertrophy of the interventricular septum and of both ventricles and obstruction of the left ventricular output.



2.2 Short axis view
Severe dilatation of the RV and severe interventricular septum with Type 3 septal curve.



2.3 PDA view
Restrictive ductus arteriosus

The recommended management focused on the management of suprasystemic PHT by maintaining iNO at 20 ppm, optimizing sedation and maintaining higher blood pressure with NE increased to 1.1 mcg/kg/min. Optimization of ventricular function was achieved through adequate ventricular filling after administering normal saline boluses to reduce the impact of biventricular hypertrophy and by supporting diastolic function through increased milrinone perfusion to 0.5mcg/kg/min. Finally, right ventricular function was improved by initiating a prostaglandins (PGE-1) perfusion to maintain ductal opening.

Follow up/ Outcome

With this treatment in place, the baby experienced a brief period of stabilization. However, at 48 hours of life, the infant had an acute clinical deterioration marked by a severe PHT crisis, presenting with profound desaturation, increased pre and post ductal saturation differences, increased FiO_2 requirements up to 80%, and hypotension (BP= 20/35mmHg, MBP of 25mmHg]). The hemodynamic team reassessed the newborn and recommended initiating vasopressin

infusion at 0.15mU/Kg/min to potentiate systemic vasoconstriction, reverse the right-to-left ductal shunting, promote pulmonary vasodilation without secondary impact on inotropy or chronotropy. Hydrocortisone was also added to address presumed adrenal insufficiency in the severely ill infant. Sedation was further optimized.

Clinical improvement was observed within one hour of initiating the vasopressin infusion, with increased arterial BP, decreased heart rate, improved urine output and reduced lactate levels (Figure 3). Oxygen requirement decreased 10 hours later, and after 12 hours of stabilization, the vasoactive medications were progressively tapered off.

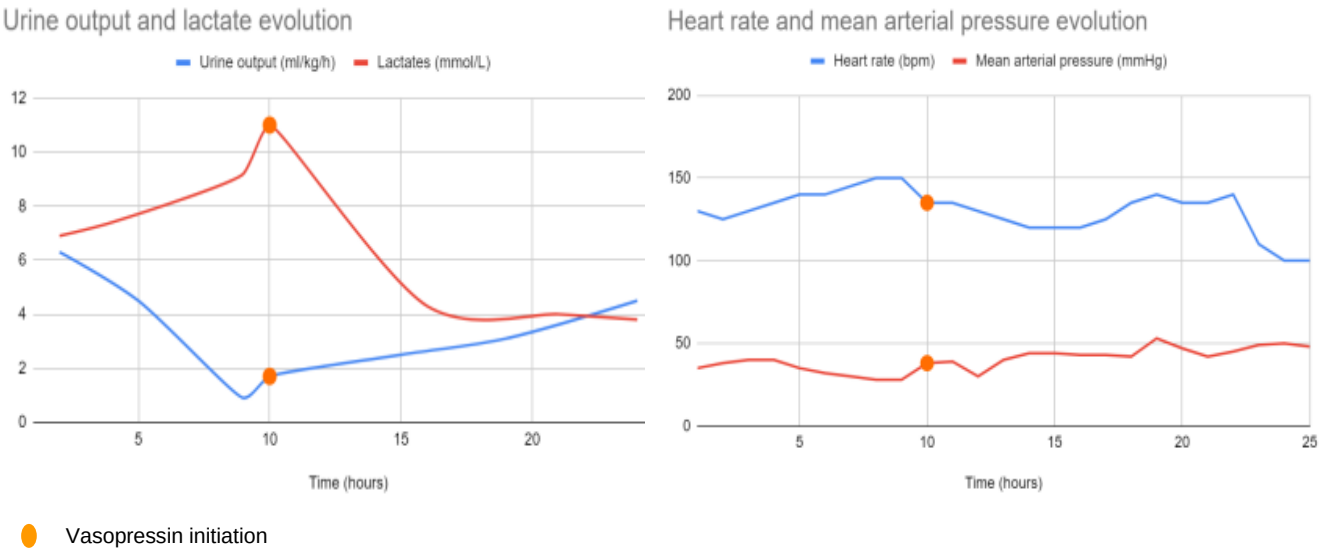


Figure 3: Changes in clinical and biological parameters after the initiation of vasopressin

The vasopressin infusion was stopped 48 hours after its initiation; however, its administration was complicated by severe hyponatremia (125 mmol/L) requiring correction with a 3% saline infusion and subsequent rebound hypernatremia (155 mmol/L) after discontinuation. The baby continued to improve, and NE infusion was discontinued at 6 days of life. A follow up TnECHO at 6 days of life showed improved but still elevated pulmonary pressures: a septal curve at 2 (Figure 4.3), a large bidirectional PDA (Figure 4.4), maximal tricuspid regurgitation jet of 52 mmHg (Figure 4.6), diastolic left ventricular function (E/A ratio = 0.8), and improved LVO (218 cc/kg/min).

Figure 4: TnECHO images at 6 days of life

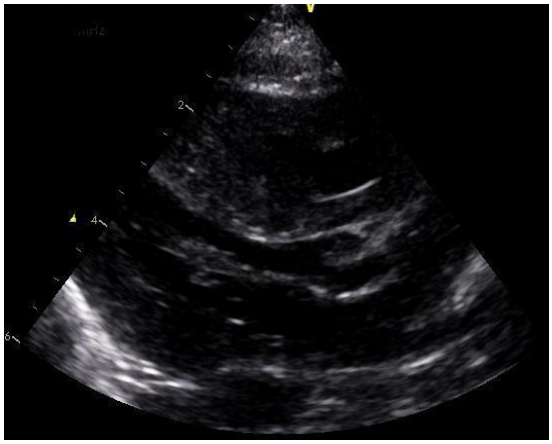


Figure 4.1 Parasternal long axis view
Better left ventricular filling

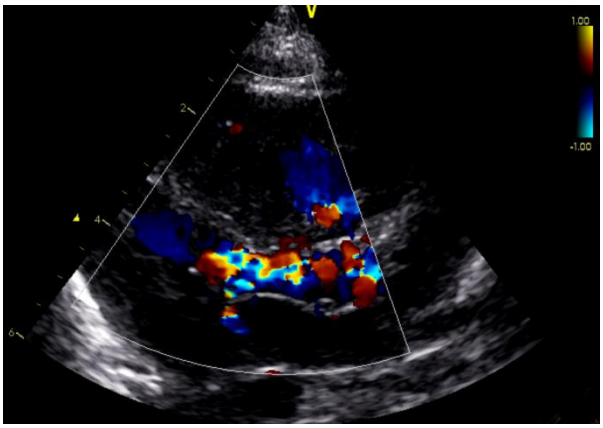


Figure 4.2 Parasternal long axis view with color Doppler. Obstruction to the left output still present. However, LVO is better

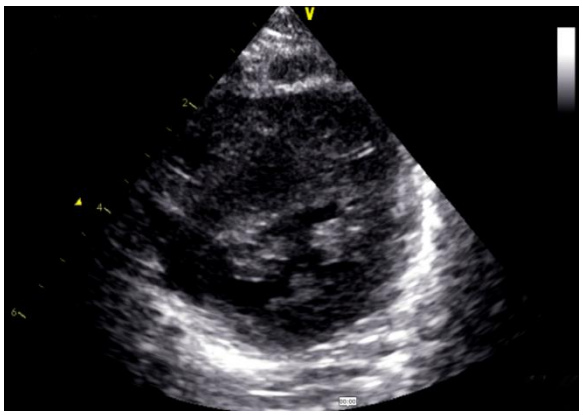


Figure 4.3 Short axis view
Type 2 septal curve and improved interventricular septum hypertrophy.

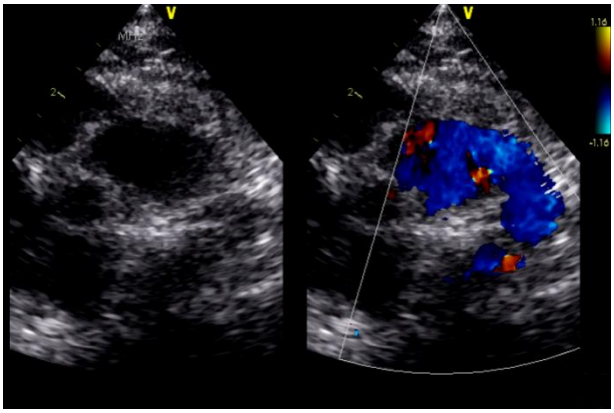


Figure 4.4 PDA view
Large PDA opened with a right to left shunt

Subsequently, the infant was extubated, and the PGE-1 and milrinone infusions were stopped. iNO was weaned off by 7 days of life, with the addition of a beta blocker to treat the persistent hypertrophic cardiomyopathy, following pediatric cardiology recommendations. At day of life 15, signs of high pulmonary pressure were still present, prompting the addition of sildenafil at 1 mg/kg/day, which was later increased to 3.5mg/kg/day. At 1 month old, just before discharge, the echocardiogram showed residual but improved biventricular hypertrophy, persistent diastolic dysfunction (inverted E/A ratio), and sub systemic pulmonary pressure. After 30 days of hospitalization, the infant was discharged home in room air and on full oral feeds, with continued sildenafil and beta-blocker treatment managed through regular outpatient pediatric cardiology follow-up appointments.

Discussion

There is an increasing trend towards higher obesity and diabetes rates among pregnant women in North America[2]. Currently, 3 to 10% of pregnancies are complicated by Type 1 or 2 diabetes mellitus or gestational diabetes[1,3]. Infants of diabetic mother (IDM) are at higher risk for neonatal complications such as macrosomia, respiratory distress syndrome, and congenital heart disease, and have up to 10 times higher mortality rates when compared to unexposed newborns.[2,4] HOCM is seen in up to 40% of IDM infants. The effects of pre-existing or gestational maternal diabetes on the fetal heart are complex and multifactorial (Figure 5). The severity of the fetal cardiac damage is related to the type of maternal diabetes, the level of HbA1C in early pregnancy, and the degree and duration of hyperglycemia and hyperketonemia[5].

In the first six weeks of gestation (period of organogenesis), hyperglycemia has a teratogenic effect inducing diabetic fetopathy, congenital cardiac malformation and fetal cardiomyopathy[1]. Subsequently, chronic intra-uterine hyperglycemia induces reflex chronic fetal hyperinsulinemia, which causes selective organomegaly, involving the heart[6-7]. In fetal macrosomia, the cardiac mass is increased due to a larger mass of myocardial nuclei, an increased number of cardiac cells, and hypertrophy of myocardial fibers. These cardiac changes lead to decreased fetal ventricular compliance and diastolic dysfunction secondary to thickened cardiac walls[1].

Prenatal screening and close follow up of diabetic mothers during pregnancy are important. Fetal echocardiography is recommended between 18 to 22 weeks of gestation[2] , and can reveal interventricular septal (IVS) hypertrophy and left myocardial wall thickness[8]. These findings are predictive of postnatal HOCM and are associated with a higher risk of fetal demise and neonatal morbidity[9]

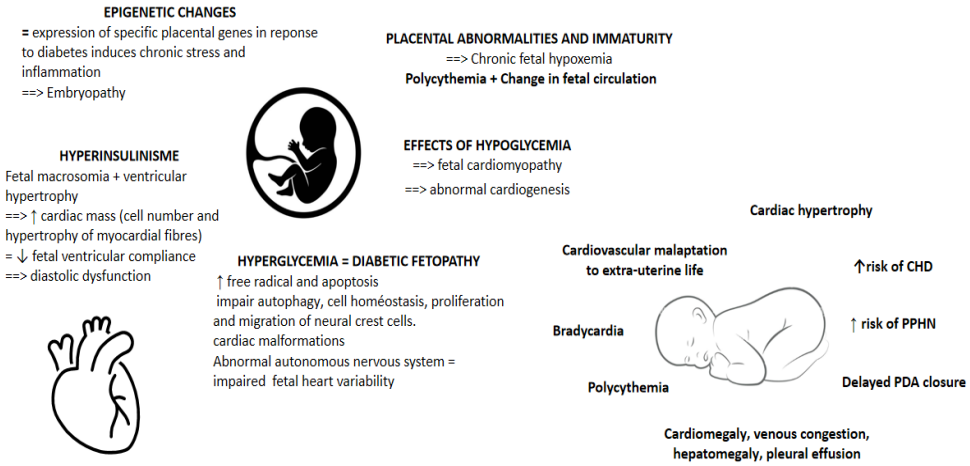


Figure 5. Effects of maternal diabetes on fetal and neonatal heart (CHD= Congenital heart disease, PPHN= Persistant pulmonary hypertension neonatal, PDA= Persistant ductus arteriosus)
Reference: Al-Biltagi, M. Cardiac Changes in Infants of Diabetic Mothers. World J. Diabetes 2021, 12

<u>Clinical and echocardiographic postnatal signs:</u>

The definition for neonatal left ventricular hypertrophy is a wall thickness of ≥ 2SD above the predicted mean corrected for body surface area (*Z-score* ≥2.0)[4]. The postnatal clinical signs of

HOCM vary from asymptomatic to refractory hypoxemia in severe cases. PHT and systemic hypotension, along with diastolic dysfunction, can occur. The postnatal echocardiography can reveal a hypertrophic, stiff, and thickened IVS and ventricular septal wall. The hypertrophy affects the ventricular relaxation, resulting in diastolic dysfunction[1]. This impaired relaxation leads to a reduction in ventricular chamber size, resulting in transient hypertrophic subaortic stenosis along with both systolic and diastolic dysfunction and mitral regurgitation[10].

TnECHO is a useful bedside tool to rapidly diagnosing and evaluating treatment response in postnatal HOCM and assessing its associated hemodynamic repercussions when facing severe hypoxemia in an IDM infant. Specifically, it enables the evaluation of the septal hypertrophy, biventricular systolic and diastolic function, pulmonary pressures[11] and evaluation for subaortic obstruction.

Table 1: Echocardiographic parameters to specifically evaluate on a patient with HOCM

Assessment	**Echocardiographic parameters**	**Echocardiographic views**
Diastolic left ventricular function	E/A mitral IVRT mitral E/e' mitral Strain ASD/PFO shunt direction and pressure gradient	Four chambers view Short axis view
LA dilation	Left atrial diameter/ Aorta diameter	Long axis view
Left ventricular cardiac output and gradient	Aortic VTI and Aortic diameter	Long axis view and four chambers view
Right ventricular cardiac output	Pulmonary VTI and pulmonary artery diameter	Long/short axis view
Pulmonary pressure assessment	Septal curve Tricuspid insufficiency jet gradient Pulmonary insufficiency gradient PDA assessment: gradient, peak pressure, direction of flow	Short axis view Long axis view/ Four chambers view Ductal view
Hypertrophy	IVS diastolic thickness	Short/long axis view

Treatment:

In most cases, HOCM is asymptomatic, and the cardiac hypertrophy recovers spontaneously within a couple of weeks. However, in more severe cases, HOCM may require neonatal resuscitation and can even lead to death. Treatment of this condition should target the underlying pathophysiology. If severe PHT is present, treatment includes adequate ventilation, iNO, optimal sedation, and maintaining blood pressure. PGE-1 infusion may be administered to maintain patency of the ductus arteriosus and help release pressure on the right ventricle to support its

function. In the presence of systolic dysfunction, inotropes may be necessary, but careful selection of agents is needed, as tachycardia can decrease the cardiac output in the setting of hypertrophy/LVOT obstruction.

LV diastolic function is an important consideration in HOCM and is supported by maintaining adequate filling volumes and regulation of heart rate by beta-blockade. Beta-blockers must be used with caution in IDM infants, as they are known to be at risk for autonomic nervous system dysregulation, so careful monitoring of heart rate and blood pressure is needed.

The addition of milrinone, in the absence of severe hypotension, has been shown to improve oxygenation index and mean arterial pressure in hypertrophic cardiomyopathy by increasing relaxation of the heart in addition to decreasing pulmonary and systemic vascular resistance[12]. Vasopressin is a potentially helpful agent in these infants, as it does not induce tachycardia and therefore will not reduce cardiac filling time and stroke volume like other sympathomimetic agents[13]. It has been demonstrated to improve the blood pressure via the V1 receptor in vascular smooth muscles. Heart rate and oxygen needs also decline after its initiation[13–15]. Vasopressin augments free renal water absorption (V2 receptor effect) and, along with systemic vasoconstriction, produces an increase in cardiac preload and afterload in the context of HOCM pathophysiology[16].

Outcome and mortality:

Newborns of diabetic mothers have better overall survival[17] compared to other neonatal etiologies for hypertrophic cardiomyopathy. Cardiac hypertrophy typically normalizes in most infants at six to twelve months of age. After discharge, those with persistent intraventricular gradient and/or those under treatment with beta blocker will be followed by the cardiology team, with frequent follow-up echocardiography. In literature, mortality in patients with HOCM is greater than in those without HOCM (4.9% vs 1.3%, $p<0.001$) and the odds of mortality also (aOR 2.10, 95% CI: 1.04-4.25; $p=0.038$)[18]. Consideration should be given to performing additional fetal echocardiography in the third trimester when diabetes is not well controlled, as this could help detect significant HOCM in the fetus before birth.

Conclusion:

As more infants are born to diabetic mothers, this population is at increased risk for severe neonatal HOCM. Symptoms of HOCM vary from mild to severe and may be associated with significant risk of neonatal mortality and morbidities. TnECHO and hemodynamic consultation are valuable tools for assessing cardiopulmonary hemodynamics associated with severe HOCM, as well as for adapting management according to initial findings and treatment response. When PHT is associated with significant HOCM, treatment with vasopressin may be considered, while closely monitoring for hyponatremia as a potential side effect of the medication. These babies must be followed by frequent hemodynamic assessment and echocardiography during neonatal hospitalization and after the discharge.

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