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Early survival following in utero myocardial infarction

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Abstract

Intrauterine myocardial infarction is a rare and frequently fatal diagnosis. It has been presented in the literature only as case reports and short series. We present a case report of a coronary occlusive intrauterine myocardial infarction and survival and present a systematic review of the literature. This is the first summative description of current data on intrauterine and perinatal myocardial infarction. We performed the systematic review based on the guidelines established by the PRISMA statement. Our population of intrauterine and perinatal myocardial infarction included published cases who presented as a live birth within the first 28 postnatal days, and had a diagnosis of myocardial infarction. We conducted descriptive statistics and regression analysis on short-term mortality as the primary outcome. After applying exclusion criteria we described 84 individual cases of myocardial infarction from 63 full-text articles including our own case. Presentation within the first 12 hours was associated with mortality (OR 3.90, $p = 0.004$). Treatment modalities were varied and inconsistently recorded. The aetiologies and comorbidities are varied in our systematic review. We would have a low threshold to perform viral testing, consider anticoagulation early and coronary imaging if feasible. The use of extracorporeal membranous oxygenation may serve as a bridge to cardiac recovery.

Intrauterine myocardial infarction is a rare and frequently fatal diagnosis. The presentation includes in utero or postnatal ventricular dysfunction, ventricular aneurysm, or postnatal haemodynamic instability. The diagnosis may not be apparent during intrauterine life. We present the case report of a newborn with an intrauterine myocardial infarction related to coronary occlusion and include a systematic review of the literature.[1–64]

Case report

During routine screening at 48 hours postpartum, a term male newborn was found to have a heart rate of 140 beats per minute by auscultation and 70 beats per minute by pulse oximetry. An electrocardiogram demonstrated ventricular bigeminy, deep Q-waves in the inferolateral leads, ST segment changes, and T-wave abnormalities (Fig 1). He was transferred to a tertiary-level paediatric ICU after identification of decreased ventricular function and a ventricular aneurysm by echocardiography. Upon arrival to the paediatric ICU, he had an intermittent gallop with good peripheral perfusion, frequent premature ventricular contractions, intermittently in a trigeminal pattern, with episodic bradycardia and hypotension.

The newborn was delivered at 37 weeks estimated gestational age to a 29-year-old multiparous mother by caesarean section secondary to fetal bradycardia. The mother had routine antenatal care without concern. The mother's only medication was a prenatal vitamin and she had no history of illegal drug use. He was vigorous at birth with APGARs of 8 and 9 at 1 and 5 minutes, respectively. There was no family history of thrombosis, miscarriage, early sudden death, or clotting disorders.

The initial echocardiogram revealed a moderately dilated left ventricle with moderately depressed systolic function with a left ventricular ejection fraction of 30.5% (normal $\geqslant 55\%$). The apex of the left ventricle was dyskinetic and aneurysmal (Fig 2). Left ventricular wall thinning of the distal lateral wall and apex was noted. Right ventricular systolic wall motion was normal with normal origins and appearance of the proximal coronary arteries (Supplementary videos 1 and 2).

Laboratory evaluation demonstrated a normal Troponin-I at 0.03 ng/ml (normal < 0.04 ng/ml) and an elevated Creatine Kinase-Muscle/Brain at 13.8 ng/ml (normal 0.6–6.3 ng/ml).

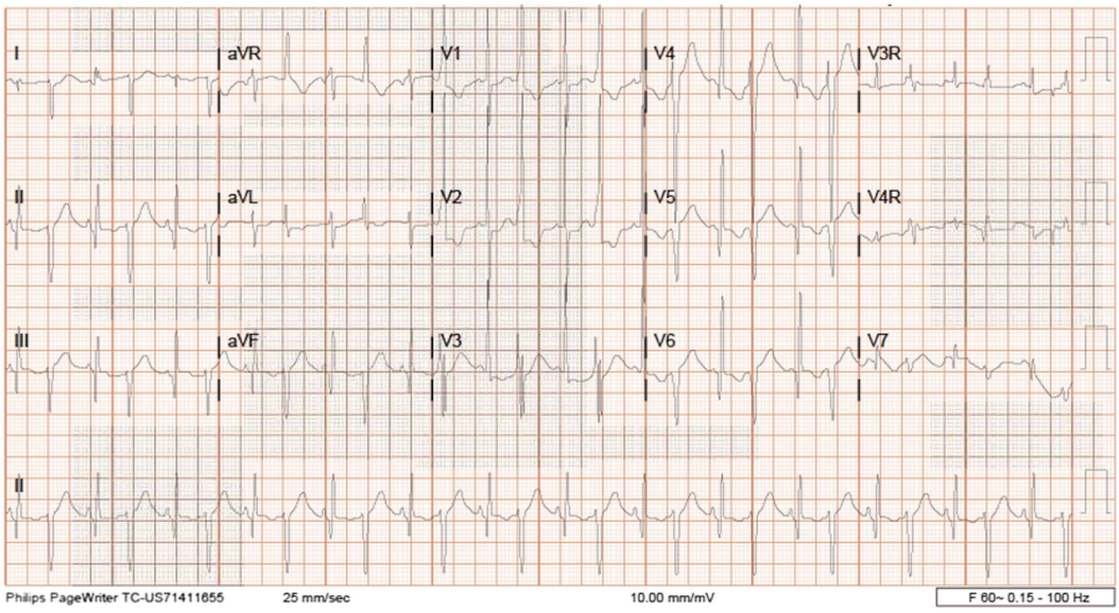

Figure 1. Electrocardiography showing ventricular bigeminy, Q-waves in the inferolateral leads, and ST segment and T-wave abnormalities.

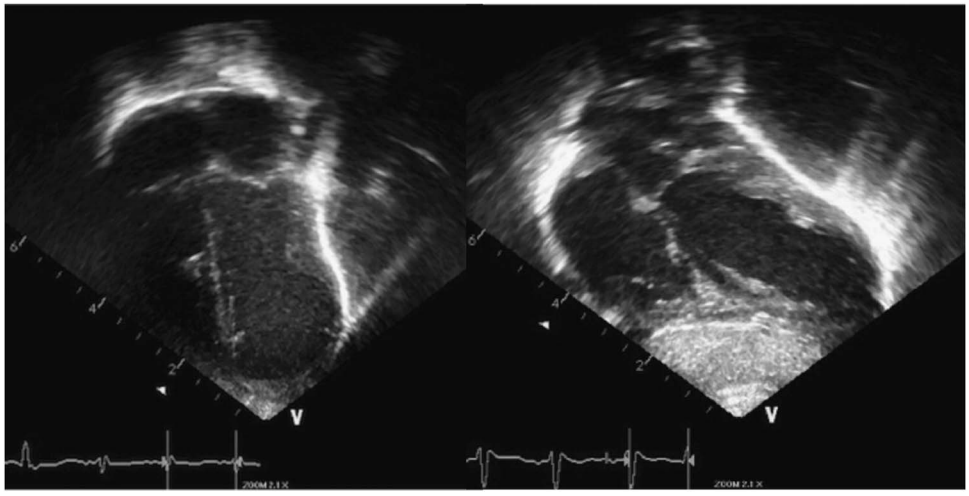

Figure 2. Echocardiogram showing a moderately dilated left ventricle and aneurysmal wall.

B-natriuretic peptide was elevated at 534 pg/ml (normal <100 pg/ml). Routine cranial and renal ultrasounds were normal. Cytomegalovirus culture and viral polymerase chain reaction studies were negative. A hypercoagulability work-up consisting of factor V Leiden, PT20210A mutation, anti-phospholipid antibodies, serum homocysteine level, anti-thrombin assay, Protein C, and Protein S was unremarkable.

An amiodarone infusion was started at 5 mcg/kg/minute. Carvedilol and captopril were initiated. The B-natriuretic peptide level decreased steadily from 534 pg/ml on day 1 to 194 and then 26 on days 4 and 7, respectively. The patient remained on low-molecular-weight heparin (enoxaparin) to reduce the likelihood of a left ventricular mural thrombus.

A repeat echocardiogram on day 7 demonstrated improvement in the left ventricular ejection fraction, increasing from 30.5 to 62.4%. Left ventricular systolic thinning and apical dyskinesis persisted. M-mode was used to estimate left ventricular ejection fraction. The same operator and cardiologist reviewed the images.

A cardiac MRI scan on day 7 confirmed normal cardiac chamber sizes with thinning of the mid-distal left ventricular lateral wall/apex with aneurysmal formation (Fig 3). There was severe hypokinesis/dyskinesis of the mid-distal lateral and apical ventricular walls. The MRI confirmed a transmural scar in the mid-distal lateral wall, a total scar burden of 15% of the left ventricle, and an ejection fraction of 38%. Right ventricular systolic function was normal. There were no other intracardiac or great vessel abnormalities.

Cardiac catheterisation with angiography was performed on day 14. The study showed normal haemodynamics on room air (Fig 4). The left anterior descending coronary artery showed abrupt occlusion near the mid-septum with two well-formed tortuous collaterals anteriorly and laterally. Angiography of the

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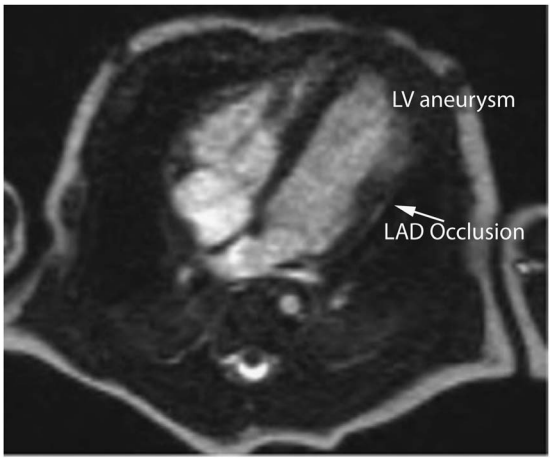

Figure 3. Cardiac MRI showing the left ventricular (LV) aneurysm and occlusion of the left anterior descending (LAD) coronary artery.

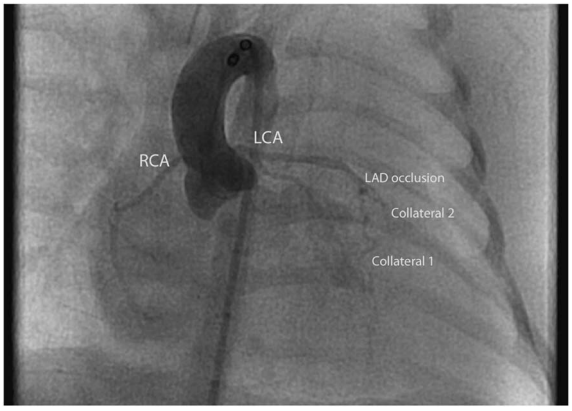

Figure 4. Coronary angiography showing abrupt occlusion of the left anterior descending (LAD) coronary artery near the mid-septum with two well-formed tortuous collaterals anteriorly (Collateral 1) and laterally (Collateral 2). Right coronary artery (RCA) and left coronary artery (LCA) identified.

right coronary artery, left main, and left circumflex arteries was unremarkable. Left ventricular systolic function had improved with a persistent aneurysmal dilation of the apex. Earlier catheterisation was considered, but there was team consensus that early angiography was unlikely to change the clinical course. Normal proximal coronary artery origins and flow had been demonstrated by echocardiography. The patient had been anticoagulated. It was felt that there was a low probability of finding coronary artery pathology that was amenable to catheter-based intervention. The decision to proceed with coronary angiography at 2 weeks after presentation was to more precisely define the coronary artery abnormality and collaterals and to assist with making a decision regarding long-term anticoagulation.

Premature ventricular contractions resolved by day 13 and the amiodarone infusion was transitioned to oral therapy. The patient was feeding well orally and gaining weight. After team discussion and before discharge on day 18, aspirin was started and enoxaparin stopped. Our choice of aspirin over enoxaparin was based on our impression that the infarct was not acute and that there was a low risk of further coronary thrombosis or left ventricular mural thrombus; thus, the risk of continuing enoxaparin was not justified. He was discharged on oral amiodarone, carvedilol, enalapril, and aspirin. The child remained asymptomatic at the 18-month follow-up visit with a persistent apical aneurysm and good left ventricular systolic function.

Systematic review introduction

Intrauterine myocardial infarction is a rare diagnosis and commonly made on autopsy in the neonatal period. To broaden our literature review, we included all myocardial infarctions diagnosed within the first 28 days after birth. Ravich et al first described neonatal myocardial infarction in 1947 and since then the diagnosis has been presented in the literature only as case reports and short series. To create a summative description of current data on intrauterine and perinatal myocardial infarction, we performed a systematic review of all published case reports.

Methods

We performed the systematic review based on the guidelines established by the PRISMA statement for reporting systematic reviews and meta-analysis of studies. In all, two authors, according to pre-determined inclusion and exclusion criteria, reviewed all studies.

We defined our population of intrauterine and perinatal myocardial infarction as those presenting within the first 28 postnatal days, a live birth, and with a diagnosis of myocardial infarction. This allowed us to exclude series of myocardial infarction diagnosed on autopsy review that would skew our results. We excluded non-English publications owing to our inability to reliably translate the full documents.

Search strategy

We searched PubMed and Ovid Medline using key terms and free text words for "myocardial infarction", "neonatal", or "newborn" or "perinatal". The Cochrane Library revealed no further relevant studies.

There were no existing meta-analyses, systematic reviews, randomised controlled trials, or cohort studies. We identified only case reports and case series. We have included data from these in our descriptive statistics and regression analysis on mortality as the primary outcome.

Studies retrieved were published from September, 1947 through January, 2016. Articles were selected for the study by screening the titles and abstracts and reviewing the full text for reaffirmation. Disagreements in study selection were resolved by consensus of all authors when necessary. Case reports that did not include data pertinent to our study were discarded.

Variables collected include gender, gestation time period (full term was defined as >37 weeks), time and type of presentation, difficult delivery/perinatal asphyxia, echocardiography use, echocardiography parameters including "regional hypokinesia", "mitral regurgitation", and "structural abnormality on echocardiography", presence of anomalous coronary anatomy, presence of dysrhythmia, documented thrombophilia, documented viral testing, presence of thrombosis and its location, use of extracorporeal membranous oxygenation, use of surgical or invasive treatment, presence of cardiac structural abnormality, survival, and co-morbidities. Difficult delivery was defined as the presence of meconium, an emergency caesarean section, abnormal cardiotocography, or the presence of a nuchal cord. We did

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not report on cardiac biomarkers or electrocardiographic findings owing to their variable reporting and lack of reference standards.

Statistical analysis

STATA version 12 was used to determine odds ratios using univariate regression analysis with short-term survival as the primary outcome measure. Statistical significance was set at the $p < 0.05$ level.

Results

A total of 579 items of literature were retrieved in our initial search of the literature (Fig 5). Two manuscripts were discarded as duplicate records. After screening titles and abstracts, 457 references were discarded owing to irrelevance or not meeting inclusion criteria. The remaining 120 articles were selected for further analysis via full-text review. Upon further review of the 120 articles, 36 articles were not included owing to not meeting inclusion criteria and another 21 articles were excluded owing to transcription in a foreign language. The decision to exclude foreign language studies was because of inadequate resources to properly translate articles for data analysis. The remaining 63 full-text articles contained 83 individual cases of myocardial infarction. We also included our own case report in the qualitative analysis, bringing the total cases studied to 84.

Population characteristics are summarised in Table 1. There is no sex preponderance – 41% were female – and the majority present early – 59% within 12 hours of birth – with profound cardiovascular dysfunction: cardiogenic shock in 56%, cyanosis in 24%, and respiratory distress in 23%. Structural cardiac abnormalities were identified in 20% (Table 2). Anomalous coronary arteries occurred in only two cases.

There is no dominant identifiable aetiology for perinatal myocardial infarction. Thrombophilia testing was performed in 20% of cases, and 29% of those were positive. Viral testing was documented in only 18% of cases, but 40% of those tested were positive for enterovirus or coxsackie virus.

Documentation of an occluded coronary artery by angiography or direct visualisation of infarcted myocardium at surgery or autopsy substantiated the diagnosis in 61 (73%). The remaining cases were diagnosed based upon a combination of electrocardiogram and echocardiogram findings and elevated cardiac enzymes. Cardiac markers included one or a combination of the following: CK, CK-MB, Troponin-I, and Troponin-T. The reporting was highly variable and was not included in this analysis. Thromboses were identified during angiography or autopsy in 32 (38%). The left coronary was involved in 26 (81%) thromboses. Extracorporeal membranous oxygenation was used in eight cases. Invasive or surgical treatment was described in 24 (29%) and included intravenous or intracoronary thrombolysis (eight cases), drainage of pericardial effusion, congenital heart surgery, valvuloplasty, and balloon septostomy. Severe co-

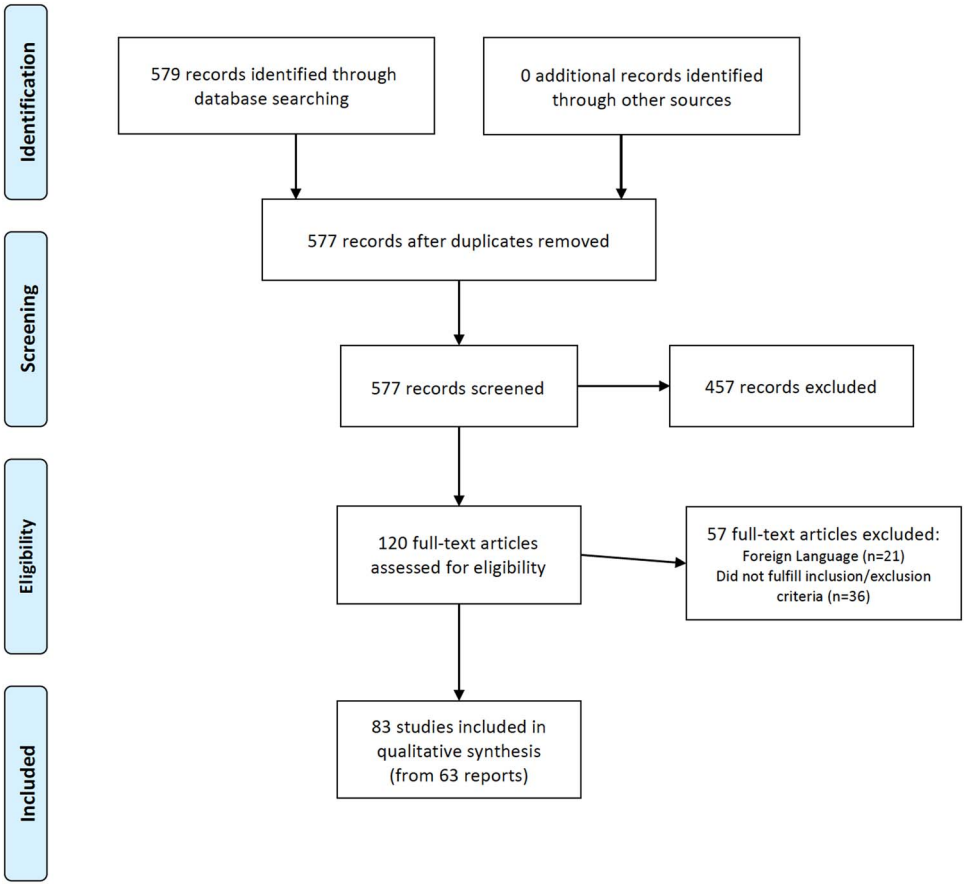

Figure 5. PRISMA Flowchart.[65]

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Table 1. Characteristics of the study population.

Characteristics	
Total number	84
Gender (n (%))*	
Male	40 (58.8)
Female	28 (41.2)
Gestational age (n (%))	
Term	61 (78.2)
Born ⩽37 weeks	17 (21.8)
Time of presentation (n (%))	
Within 12 hours	50 (59.5)
12 hours or after	34 (40.5)
Presentation patterns (n (%))	
Cardiogenic shock	47 (56.0)
Cyanosis	20 (23.8)
Respiratory distress	19 (22.6)
Cardiac failure	5 (6.0)
Arrhythmia	4 (4.8)
Other**	15 (17.9)
Delivery (n (%))***	
Difficult delivery/perinatal asphyxia****	19 (23.2)
No documented difficulty	63 (76.8)
Echocardiography use (n (%))*****	53 (63.1)
Coronary anatomy (n (%))	
Anomalous coronaries	2 (2.4)
Normal coronaries	80 (95.2)
Anatomy not documented	2 (2.4)
MI diagnosis (n (%))	
Visually confirmed******	61 (72.6)
ECG, ECHO, labs only	23 (27.4)
Confirmed thrombus (n (%))*******	
Left coronary or its branches	26 (81.3)
Right coronary	3 (9.4)
Aorta	1 (3.1)
Multiple locations	2 (6.2)
Dysrhythmia (n (%))********	
Yes	20 (23.8)
Not documented	64 (76.2)
Thrombophilia (n (%))*********	
Positive testing	5 (29.4)
Negative testing	12 (70.6)
Viral testing (n (%))**********	
Positive testing	6 (40.0)
Negative testing	9 (60.0)
ECMO use (n (%))	
Yes	8 (9.5)
Not documented	76 (90.5)
Invasive or surgical treatment (n (%))***********	
Yes	24 (28.6)
Not documented	60 (71.4)
Survival (n (%))	
Yes	38 (45.2)
No	46 (54.8)

ECG = electrocardiography; ECHO = echocardiography; ECMO = extracorporeal membranous oxygenation.
*Gestational age was documented in 78 cases.
**The "other" presentations included apnoea, hypotonia, hypothermia, maternal pre-existing condition, prenatally identified heart disease, asphyxia, and vomiting.
***Perinatal asphyxia or a difficult delivery was documented in 19 of 82 cases.
****Difficult delivery was defined as the presence of meconium, an emergency caesarean section, abnormal cardiotocography, or the presence of a nuchal cord.
*****Echocardiography was not available in 31 cases, all published between 1947 and 1986.
******Confirmation of infarction was by angiography or direct visualisation at surgery or autopsy. Other myocardial infarctions (MI) diagnoses based on one or a combination of the following: ECG, ECHO, and elevated cardiac markers only.
*******Identifiable thromboses were identified during angiography or autopsy in only 32 cases (38%).
********Dysrhythmia included bradycardia, heart block, wide complex tachycardias, supraventricular, and junctional tachycardias and ventricular ectopics.
*********Thrombophilia testing was documented only in 17 cases.
**********Viral testing was only documented in 15 cases.
***********Invasive or surgical treatment included intravenous or intracoronary thrombolysis (eight cases), drainage of pericardial effusion, exchange transfusion, congenital heart surgery, valvuloplasty, and balloon septostomy.

morbidities were described in 29 (35%) (Table 3). Overall, 38 (45%) newborns survived.

Systematic review analytics: association between patient characteristics and mortality in a series of published case studies.

Presentation within 12 hours and lack of echocardiogram were statistically associated with mortality ($p = 0.004$ and <0.001, respectively). The majority lacking echocardiograms were cases reported in the years before it was standard of care. Mortality was associated with female gender ($p = 0.051$), approaching significance. Perinatal asphyxia has been shown to raise troponin-T and impair systolic myocardial function.[66] However, among newborns with myocardial infarction, the presence of a difficult delivery or perinatal asphyxia was not associated with increased mortality (Table 4).

Discussion

Coleman first described intrauterine myocardial infarction in 1962, with subsequent reports associated with stillbirth and

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Table 2. Identified cardiac structural abnormalities.

Supravalvular aortic obstruction (thrombus)
No antegrade flow across aortic valve (n = 2)
Hypertrophic cardiomyopathy
Ventricular septal defect (VSD)
Aortic arch hypoplasia
Pulmonary valve atresia, hypoplastic right ventricle (n = 2)
Aortic atresia
Tricuspid atresia (VSD (n = 2))
Aneurysm of the posterior diaphragmatic wall
Hypoplastic left heart syndrome (n = 2)
Anomalous left coronary from right coronary
Pulmonary atresia with intact ventricular septum

Table 3. Identified co-morbidities.

Multiorgan failure
Necrotising enterocolitis
Hydramnios, septal hypertrophy (maternal diabetic complications)
Cerebral infarction
Severe jaundice requiring exchange transfusion
Multiorgan infarction/haemorrhage
Trisomy 21
Thrombocytopaenia, seizures, cerebrovascular accident
Cardiac arrest
Congenital diaphragmatic hernia
Endocarditis
Pulmonary atresia, intact ventricular septum, hypoplastic RV
Bilateral adrenal vein thromboses
Chronic pancreatitis, pulmonary haemorrhage
Maternal cannabinoid/methadone/cocaine abuse
Rhesus incompatibility and hydrops fetalis
Enteroviral meningitis
Chorioamnionitis
MSSA/Klebsiella bacteraemia
Grade IV intraventricular haemorrhage
Aortic atresia
Haemorrhage with anaemia (2.5 g/dl)
Haemoglobin H disease
Bronchopulmonary dysplasia, cerebral palsy
Sigmoid haemorrhage and perforation of sigmoid colon
Tricuspid atresia

MSSA = methicillin sensitive staphlococcus aureus; RV = right ventricle.

hydrops fetalis in twin gestations.[30,67,68] Survival has only been described once before in published reports of specifically intrauterine myocardial infarction.[51]

Intrauterine myocardial infarction studies (Table 5)

Aetiology

Our data on in utero and perinatal myocardial infarction support the polyfactorial association with thrombus, underlying thrombophilia, viral myocarditis, and those with severe co-morbidities. Anomalous coronary anatomy is a rare cause of myocardial infarction in the perinatal period (Table 5).

Presentation

Common perinatal presentations include acute cardiogenic shock, cyanosis, and/or respiratory distress. Of the cases with identifiable thrombus, 81% involved the left coronary artery and its tributaries. This may not be evident during fetal life because of the relatively lower metabolic demand of the left ventricle. Paradoxical thromboembolism from the umbilical venous system has been suggested in other case reports. Of the 32 cases with identified thrombus, three cases also found thrombi in the ductus venosus or umbilical veins. An additional three cases had thrombi within the cardiac veins, suggesting that the diagnosis of thromboemboli is underestimated.

Diagnosis

Elevated cardiac biomarkers have been described to occur in otherwise healthy term and preterm newborns, peaking on day three.[69,70] Elevated Troponin-T levels have been described in respiratory distress syndrome, grade III neonatal encephalopathy, and perinatal asphyxia with variable cardiac impairment.[71,72] Troponins also appear to be a surrogate marker of global hypoxia/ischaemia.[70] Highly sensitive cardiac Troponin-I has not yet been evaluated as an aid for diagnosis in paediatric myocardial infarction. Given the unquantified influence of gestational age, birth weight, gender, and delivery on cardiac biomarker reference ranges in the neonatal population, it remains challenging to separate normal neonatal physiologic myocardial remodelling from either myocardial injury or true infarction. Electrocardiographic criteria for the diagnosis of acute myocardial infarction in childhood have been suggested.[73] However, the similar confounding issues of myocardial strain during normal physiologic adaptation or relative myocardial injury due to global hypoxia/ischaemia raise concerns over its utility during the perinatal period.

Certain laboratory, electrocardiographic, and echocardiographic findings may suggest a diagnosis of neonatal myocarditis, as well as acute myocardial infarction.[32] Myocarditis has been postulated as a potential aetiology for intrauterine myocardial infarction. Localised inflammation may result in coronary arteritis and thrombosis. Myocarditis should be considered not only in the differential diagnosis in the setting of a potential intrauterine myocardial infarction but also as a possible underlying cause.

Clinical management focusses on the management of haemodynamic derangements and arrhythmias. Tissue plasminogen activator has been used in the setting of suspected acute infarction. Extracorporeal membranous oxygenation may have a role as

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Table 4. Systematic review analytics: association between patient characteristics and mortality in a series of published case studies.

	Odds ratio	95% Confidence intervals	p value
Gender			
Male (Referent)			
Female	2.70	(0.99–7.33)	0.051
Presentation			
12 hours or more after birth (Referent)			
Within 12 hours	3.90	(1.55–9.78)	0.004
Prematurity			
Term birth (Referent)			
Premature birth (⩽37 weeks gestation)	1.02	(0.35–2.99)	0.972
Delivery			
Documented uncomplicated delivery (Referent)			
Difficult delivery/perinatal asphyxia	1.56	(0.59–4.12)	0.374
ECHO availability			
ECHO use documented (Referent)			
Lack of ECHO	8.58	(2.84–25.95)	<0.001
Cardiac structure			
ECHO performed with normal structure (Referent)			
Structural abnormality on ECHO	3.00	(0.85–10.56)	0.087
ECMO			
ECMO used (Referent)			
ECMO use not documented	4.12	(0.78–21.78)	0.095
Tissue plasminogen activator (tPA)			
tPA use documented (Referent)			
tPA not used	2.17	(0.48–9.75)	0.311

ECHO = echocardiography; ECMO = extracorporeal membranous oxygenation.

Table 5. Intrauterine myocardial infarctions studies.

Study	Survival	Coronaries	Thrombus	Diagnosis	Other findings
Coleman and Macdonald[30]	Died	Normal	Adherent to wall of RV	Infarction at autopsy	None
Birnbacher et al[51]	Survived	Normal	None	99mTc-sestamibi perfusion scan	LV aneurysm
Marton et al[67]	Died	Thickened walls	None	Termination and autopsy	Hydrops fetalis, twin–twin transfusion
Concheiro-Guisan et al (2006)[74]	Died	Coronary ostium stenosis and hypoplastic left coronary artery	None	Infarction at autopsy	Abdominal aortic thrombus
Volker et al[68]	Died	Normal	None	Infarction at autopsy	None

LV = left ventricle; RV = right ventricle.

a bridge to cardiac recovery. The number of patients treated with extracorporeal membranous oxygenation or tissue plasminogen activator was insufficient to provide the power to detect a statistically significant clinical contribution. Treatment modalities were varied and inconsistently recorded. Limited by the study's retrospective nature, we found no treatment modality trend in the systematic review. There were no long-term follow-up or neurodevelopmental outcomes recorded.

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Our own case highlights the wide differential for ischaemia in a neonate. The aetiologies and associated co-morbidities are varied, as highlighted in the systematic review. Our patient continued to improve with medical management only. We would suggest having a low threshold to perform viral testing, consider anticoagulation early, and coronary imaging if feasible.

Limitations

Systematic reviews of case reports are rarely performed because of the limitations of retrospective data and risk of publication bias. However, the rarity of neonatal/perinatal myocardial infarction would make obtaining meaningful data from a single centre or prospective study difficult. Our systematic review was designed to present summative data and describe clinical and diagnostic characteristics not previously described in large numbers.

We are limited by the retrospective nature of the project on which conclusions we can draw. We would highlight that electrocardiographic and lab values suggestive of infarction may also indicate myocarditis or an alternate diagnosis with associated myocardial dysfunction. We included these more equivocal cases as we were unable to state that ischaemia was not present.

Conclusions

Intrauterine and neonatal myocardial infarctions are extremely rare. The diagnosis should be considered in the setting of cardiovascular instability or arrhythmia in the newborn period. Viral myocarditis may mimic laboratory and electrocardiographic changes of a myocardial infarction. The use of extracorporeal membranous oxygenation may serve as a bridge to cardiac recovery.

Supplementary materials. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951118001105

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Conflicts of Interest. None.

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