

Premature foetal closure of the arterial duct: clinical presentations and outcome

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Aims

The prevalence of intra-uterine ductal dysfunction is unknown and the clinical consequences are poorly understood. The aim of this study was to investigate the echocardiographic (ECHO) abnormalities and outcomes of this rare phenomenon.

Methods and results

Retrospective analysis of foetal ($n = 602$) and neonatal ECHO databases ($n = 1477$) between 1998 and 2007. Clinical and imaging studies were reviewed for pathology due to or associated with premature closure of the duct. Twelve cases were identified. Eight (1.3%) were diagnosed pre-natally at a median gestational age of 29.0 weeks (range: 20.0–37.5 weeks). Four neonates (0.3%) with significant cyanosis and absence of the arterial duct were also included. The most common ECHO features were: excessive right ventricular (RV) hypertrophy (100%), more than expected tricuspid and pulmonary regurgitation (100% and 92%, respectively), and right atrial dilation (75%). Premature induction of delivery was advised for five patients. Neonatal therapy consisted of observation and oxygen administration ($n = 7$), ventilation with pulmonary vasodilators ($n = 5$), and one required extracorporeal membrane oxygenation. There were three deaths due to respiratory failure with severe pulmonary hypertension. During follow-up, two children required additional right heart procedures and one developed a non-compaction cardiomyopathy.

Conclusion

Foetal premature closure of the arterial duct causes stress at different foetal ages and many different levels of the right heart and pulmonary circulation, resulting in a wide range of secondary pathology. Disproportionate RV hypertrophy is the most common finding. Clinical outcomes range from mild symptomatology to lethal respiratory insufficiency.

Keywords

Ductus arteriosus • Premature closure • Pre-natal diagnosis • Ultrasound • Disulfiram • Non-steroidal anti-inflammatory drugs

Introduction

Intra-uterine dysfunction of the ductus arteriosus is an acknowledged event, but seems to be a rare phenomenon. The majority of the cases are probably subclinical or mildly symptomatic and therefore not diagnosed. In only few cases will ductal dysfunctions come to the attention of the foetologist, neonatologist, or paediatric cardiologist. Literature regarding this entity is scant and essentially consists of anecdotal case reports. These reports have mentioned cardiovascular dysfunction such as (transient neonatal)

tricuspid regurgitation, pulmonary regurgitation, dilation of the pulmonary trunk, the right ventricle (RV) and the right atrium, excessive RV hypertrophy, functional pulmonary atresia, absent pulmonary valve syndrome, hydrops foetalis with possible foetal demise, and persistent neonatal pulmonary hypertension.^{1–6}

The ductus is an important structure during foetal life as it allows unloading of the RV and joins the pulmonary trunk to the aorta with a diameter equivalent to these two major vessels.⁷ The foetal RV ejects 60–65% of the combined cardiac output, of which 90% is shunted via the ductus to the aorta.² The physiology

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Table 1 General summary of patients

	GA first visit	Maternal factors	Dominant ECHO finding	Delivery	GA birth (weeks)	Birth weight (g)	Treatment	Outcome
Foetal								
1	37		RV dysfunction, PA dilatation	Spontaneous	38	2930	Oxygen	A
2	34	NSAID	RVH	Spontaneous	Term	3220	Ventilation	D Day 3
3	27		Hydrops, TR	Premature induction	30	1780	Ventilation	A Cardiomyopathy
4	34	NSAID	TR, RVH	Premature induction	35	1800	Ventilation	D 24 h
5	32		RV, RA massive dilatation	Premature induction	34	2700	Oxygen	A
6	20		PA dilatation, cystic lung	Spontaneous	39	3500	Ventilation	D 3 h
7	28		PA dilatation, PR	Premature induction	37	2760	Oxygen	A Homograft PA
8	28	NSAID (20 weeks)	RVH, TR	Premature induction	37	2300	Oxygen	A PS, ASD
Neonatal								
1			RVH, TR		Term	3500	Oxygen	A
2		Disulfiram	RVH, ductal thrombus		Term	3720	Ventilation	A Surgery Day 12
3			TR, RVH		Term	2920	Oxygen	A
4			RA, RV dilation, TR		Term	3650	ECMO	A

Overview and general summary of case details. GA, gestational age; NSAID, non-steroidal anti-inflammatory drug; RV, right ventricle; RVH, right ventricle hypertrophy; PA, pulmonary artery; TR, pathological tricuspid regurgitation; PR, pathological pulmonary regurgitation; A, alive; D, death; PS, pulmonary stenosis; ASD, atrial septal defect. See text for details.

and structure of the ductus differs considerably from the two adjacent vessels:^{8,9} the ductus has a predominantly muscular media with circumferential fibres and a well-defined internal elastic lamina. Towards term endothelial cushions develop which are involved with closure after birth. Prostanoids and low foetal oxygen saturations play an important role in maintaining ductal patency during foetal life.^{10,11} The structure and shape of the ductus both vary during foetal life: initially it is quite long and then becomes tortuous with changing of the angles of attachment to the aorta.^{12,13} It therefore stands to reason that dysfunction of the foetal ductus may occur due to numerous factors and may have a profound effect on the cardiovascular system.

This study was undertaken to determine the different forms of echocardiographic (ECHO) abnormalities, the presentation during foetal and neonatal life, as well as the clinical outcomes of this entity.

Methods

This is a retrospective, single-centre study. Foetal and neonatal cardiac databases from 1998 to 2007 were searched: 602 fetuses were referred because gross abnormalities of either the heart or great vessels, or associated structures were detected during routine antenatal screening. The local congenital cardiac database was also searched: 1477 echocardiograms were performed in neonates within the first 24 h of life.

Echocardiograms were reviewed to identify lesions where ductal dysfunction may have been the cause. Closure of the ductus arteriosus was confirmed if the ductus was absent on standard two-dimensional views and colour and/or pulsed-wave Doppler interrogation showed no flow.¹⁴ Only cases with echocardiographically confirmed closure of the foetal ductus arteriosus were included. Neonates were included if they presented with significant cyanosis due to atrial right to left shunt and excessive RV hypertrophy; closure of the ductus arteriosus had to be confirmed within 24 h after birth. This definition is in agreement with other published reports.¹⁵ In both groups, patients with overt congenital cardiac pathology (e.g. tetralogy of Fallot, ventricular septal defect, etc.) were excluded. All abnormalities were noted and data entered into standard Microsoft Excel[®] spreadsheets for analysis.

Results

There were 12 patients identified with pathology due to or associated with premature closure of the ductus arteriosus. Eight prenatal cases (8/602 = 1.3%) were included. Gestational age at presentation in this group ranged from 20.0 to 37.5 weeks with a median of 29.0 weeks. An additional four post-natal cases (4/1477 = 0.3%) were identified with cyanosis due to pre-natal ductal dysfunction. Echocardiography performed within 24 h confirmed the absence of a patent arterial duct.

Patient characteristics are summarized in Table 1. Table 2 lists the important ECHO findings. Marked RV hypertrophy was seen in all cases. More than trivial, tricuspid valve regurgitation was

also found in every patient. Moderate to severe pulmonary regurgitation and right atrial dilation were present in most patients. Pulmonary artery dilatation was also seen in five cases. Post-natally, excessive apical RV hypertrophy leads to the additional diagnosis of bipartite RV in a considerable number of patients (75%) (Figure 1). All four neonates presented at birth with cyanosis and excessive RV hypertrophy. Three mothers received non-steroidal

anti-inflammatory drugs (NSAIDs) during pregnancy, two in the third and one in the second trimester. In one, disulfiram was implanted before pregnancy.

Five cases are described in more depth as an example of the findings.

Foetus 4

A routine foetal echocardiogram was performed at the age of 22 weeks since a sibling had hypoplastic left heart syndrome. Echocardiography at this stage was reported as normal. At 34 weeks of gestational age, marked RV hypertrophy was observed (free wall, 6–7 mm; normal, <3–4 mm) (Figure 2). There was significant tricuspid regurgitation with a flail valve. The pulmonary valve was moving but hardly opened, without any significant flow noticed in the pulmonary trunk. The arterial duct was closed. The mother had taken an NSAID a couple of days prior to the examination. The child was born by elective induction at 35 weeks; birth weight 1800 g. Immediate ventilation was required because of significant cyanosis. An echocardiogram performed at the age of 45 min demonstrated significant RV hypertrophy and dilation as well as important tricuspid valve regurgitation with prolapse of the septal leaflet of the tricuspid valve (probably muscle rupture). There was minimal anterograde pulmonary artery flow and the right atrium decompressed through the foramen ovale to the left atrium (functional pulmonary atresia). The arterial duct was closed. Despite intensive treatment, post-natal cyanosis persisted with significant pulmonary hypertension and respiratory failure. Extracorporeal membrane oxygenation (ECMO) was not possible at that stage (too small—1800 g) and the neonate died at the age of 6 h. Autopsy showed a fibrotic ductus, proof of antenatal closure. The pulmonary valve was normal.

Foetus 5

Foetus 5 was referred at 32 weeks post-menstrual age because of a 'small left heart'. However, detailed evaluation showed a normal-sized left heart; in contrast, the right heart was markedly dilated with significant RV hypertrophy and tricuspid regurgitation

Table 2 Echocardiographic findings

Finding	Number (n)	%
Right atrium		
Dilation	8	75
Tricuspid valve regurgitation (moderate–severe)	12	100
Right ventricle		
Hypertrophy	12	100
Bipartite	8	75
Pulmonary valve		
Stenosis	2	17
Regurgitation (moderate–severe)	11	92
Dysplastic	3	25
Pulmonary artery		
Dilatation trunk and branch pulmonary arteries	5	42
Foetal suprasystemic pulmonary pressure (measurement TR)	2	17
Functional pulmonary atresia	1	8
Other		
Pericardial effusion	1	8
Aneurysm ductus with thrombus	1	8
Hydrops foetalis	1	8
Microcystic lung changes	1	8

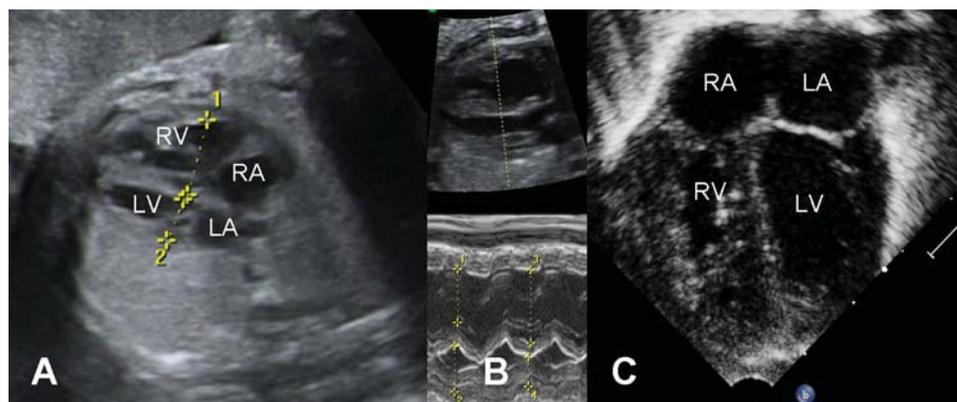


Figure 1 Foetus 5. (A) Foetal four-chamber view showing a dilated, hypertrophic RV. (B) Foetal longitudinal view with M-mode showing marked RV hypertrophy. (C) Neonatal echo: the RV had evolved from 'dilated' to 'collapsed'. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

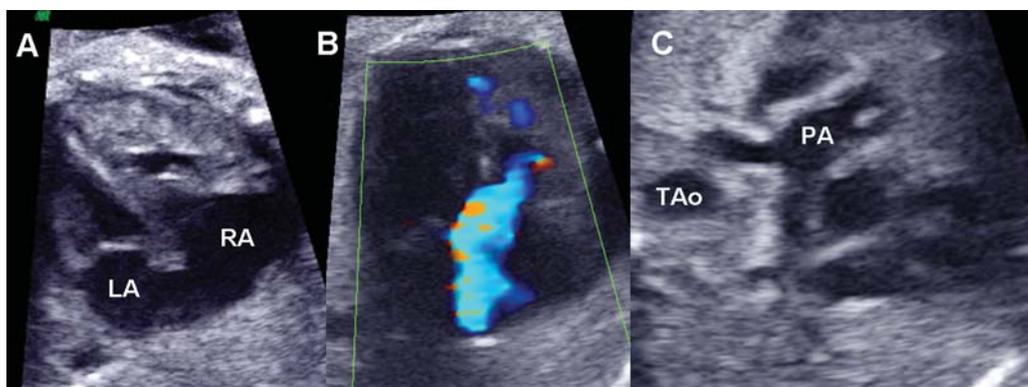


Figure 2 Fetus 4. (A) Excessive right ventricular hypertrophy anterior wall 6–7 mm. (B) Due to flail tricuspid valve significant tricuspid valve regurgitation. (C) 'Postnatal' type of bifurcation of pulmonary artery without any connection to the thoracic aorta. TAo, thoracic aorta.

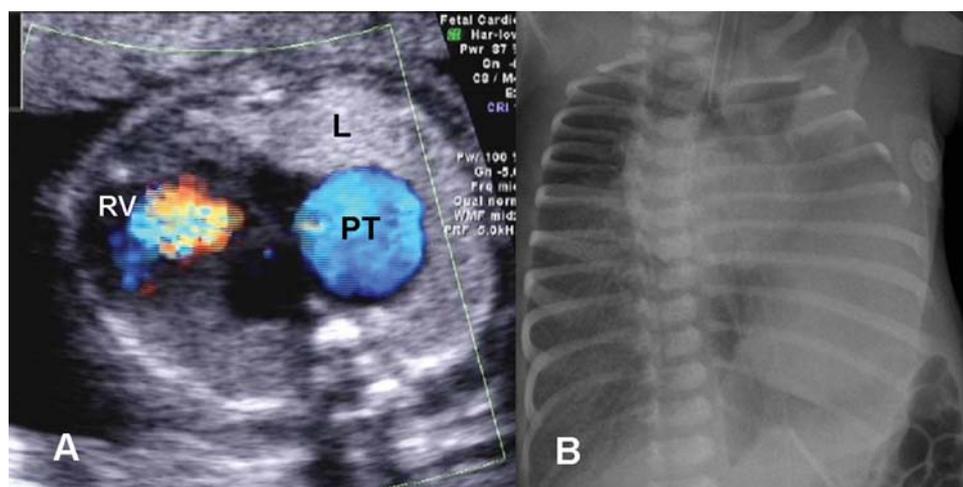


Figure 3 Foetal echocardiogram at 34 weeks of foetus 6. (A) Foetal echocardiogram showing cardiomegaly, a dilated pulmonary trunk, and hyperechogenic microcystic lungs. (B) Neonatal chest X-ray: excessive airtrapping causes hyperinflation with downward shift of the diaphragm, the heart is pedunculated. L, lung; PT, pulmonary trunk; RV, right ventricle.

(Figure 1A). No arterial duct could be identified. Sequential follow-up demonstrated progressive tricuspid valve regurgitation. The foetus was delivered prematurely by elective caesarean section at 34 weeks post-menstrual age. An echocardiogram performed within 1 h after birth showed a small RV cavity with significant hypertrophy and the apex completely filled-up by muscle, no ductal shunt. The RV had evolved from a dilated, pressure-overloaded chamber before birth to a hypertrophic, 'collapsed' bipartite chamber after birth (Figure 1C). The neonate was treated with oxygen administration only. Outcome was good with the regression of RV hypertrophy and growth of the RV cavity over the following weeks.

Foetus 6

Foetus 6 presented at post-menstrual age of 20 weeks: she had significant pulmonary regurgitation with aneurismal dilatation of the

pulmonary trunk (Figure 3A). The RV was hypertrophic, dilated, and hypocontractile, with tricuspid regurgitation. Detailed examination failed to identify a patent arterial duct. Starting at 23 weeks, sequential echocardiograms during follow-up demonstrated a hyperechogenic microcystic appearance of the lungs. Different options were discussed with the parents seeing that a dismal outcome was expected, but they preferred spontaneous evolution. Delivery was uneventful. After transection of the umbilical cord, the neonate developed significant cyanosis despite intubation and ventilation. Cyanosis persisted with percutaneous oxygen saturations of 30%. Significant respiratory failure developed with a PaCO_2 in excess of 80 mmHg. Chest radiography showed dramatic air trapping (Figure 3B). An echocardiogram performed 30 min after birth showed the absence of the duct. The neonate died at the age of 3 h. Autopsy was refused by the parents.

Foetus 7

Foetus 7 presented at 20 weeks post-menstrual age with significant RV hypertrophy, mild pulmonary stenosis, and severe pulmonary regurgitation, as well as marked dilatation of the pulmonary trunk. There was no arterial duct. The pregnancy was continued until 37 weeks. At birth, the neonate had mild cyanosis which improved with oxygen administration. Echocardiography demonstrated significant RV hypertrophy (7 mm), disproportionate to the degree of pulmonary valve stenosis (gradient = 57 mmHg). Pronounced pulmonary valve regurgitation with a dilated pulmonary trunk of 21 mm was also present. No duct could be identified. The child did well, with spontaneous normalization of arterial oxygenation within 1 week. Post-natal diagnosis of 'agenesis of pulmonary valve' was made. At the age of 30 months, a 17 mm homograft was implanted in the RV outflow tract, with reduction-plasty of the pulmonary trunk and left pulmonary artery.

Neonate 2

Neonate 2 presented with significant cyanosis and a hoarse voice at birth. The mother had disulfiram (Antabuse®) implanted prior to the pregnancy. No pre-natal ECHOs were performed. On admission, at the age of 4 h, the ECHO showed significant RV hypertrophy, tricuspid regurgitation, and pulmonary valve regurgitation. There was a multi-layered mass in the ductal region, protruding and obstructing the origin of the left pulmonary artery. A tentative diagnosis of aneurismal dilatation of the duct with secondary thrombosis was made. Magnetic resonance imaging confirmed a thrombus in the duct. The patient was referred for surgery in order to reopen the left pulmonary artery. The aneurism and thrombus were completely resected on Day 12. The patient did well post-operatively. Microscopic examination of the resected specimen showed the recurrent nerve to be completely entrapped within the walls of the aneurism of the duct.

Patient management

On the basis of progressive RV dilatation and tricuspid regurgitation, early termination of pregnancy (35.0 ± 2.9 weeks) was performed in five of eight foetal cases in order to avoid further damage to the right heart and pulmonary vasculature. Management issues and outcomes are summarized in Table 3. Observation and oxygen administration via head box was the only treatment required in 7 of 12 of the neonates. The other neonates ($n = 5$) presented with severe cyanosis and required mechanical ventilation as well as administration of pulmonary vasodilators. Two infants received nitric oxide, one for 1 day only and the other for 11 days. One neonate was severely hypoxic and acidotic and therefore ECMO was instituted with good outcome. As mentioned, one child required neonatal surgery on Day 12 due to obstruction of the left main pulmonary artery. Respiratory insufficiency and severe pulmonary hypertension were the cause of death in three neonates.

Follow-up

Cardiovascular sequelae were noted in three patients: one patient needed balloon angioplasty of significant pulmonary stenosis at the age of 7 months, followed by percutaneous closure of an atrial

Table 3 Management and outcomes

	Number (n)	%
Foetal		
Premature induction of delivery	5	62
Neonatal treatment		
Observation and oxygen administration	7	58
Ventilation with administration of pulmonary vasodilators	5	42
ECMO	1	8
Surgery		
Resection thrombosed aneurismal ductus—occlusion LPA	1	8
Outcome/follow-up		
Neonatal death	3	25
Cardiovascular		
Balloon angioplasty of PS (7 months) and closure ASD (9 years)	1	8
Homograft reconstruction pulmonary artery	1	8
Cardiomyopathy (non-compaction)	1	8
Psychomotor delay, mild	2	17

ECMO, extracorporeal membrane oxygenation; LPA, left pulmonary artery; PS, pulmonary valve stenosis; ASD, atrial septal defect. See text for details.

septal defect at the age of 9 years. Another patient had homograft reconstruction of the RV outflow tract with reduction angioplasty of the pulmonary arteries at the age of 3 years. One patient who presented with hydrops first 'normalized' his cardiovascular system after birth; however, at the age of 4 years, he presented with left heart dysfunction and non-compaction cardiomyopathy. Two patients developed mild psychomotor impairment.

Discussion

This study confirms that premature closure of the ductus arteriosus may occur during foetal life and can have profound and diversified effects on different levels of the right heart. Right ventricular hypertrophy disproportionate to the presumed functional status was present in all cases. Dilatation of the right atrium and ventricle as well as moderate to severe tricuspid- and pulmonary valve regurgitation with dilatation of the distal pulmonary arteries were some of the most frequent abnormalities found on ECHO. This study broadens and further refines the reported clinical spectrum of pathology caused by premature closure of the duct: rupture of tricuspid valve chordae with flail valve, association with clinical entities such as 'bipartite RV' and 'agenesis of pulmonary valve syndrome' in its most extreme form with amniotic fluid and air trapping, neonatal respiratory insufficiency due to pulmonary hypoperfusion or ventilatory insufficiency, and late cardiac pathology. Intra-uterine death was not observed in this series.

Presumed pathophysiology

Premature closure of the foetal ductus will result in an immediate increase in afterload of the RV with resultant hypertrophy,

dysfunction, dilation, tricuspid valve regurgitation, papillary muscle stress, and ischaemia, sometimes resulting in papillary muscle rupture with flail valve.^{2,3,15,16} An increase in pulmonary trunk pressure may change blood flow in the high-resistance, fluid-filled lungs.¹⁷ The intra-uterine increase in pressure leads to hypertrophy of the media, causing pulmonary hypertension and post-natal persistent pulmonary hypertension of the neonate.^{2,5} After birth, this combination of pulmonary hypertension, RV dysfunction, and tricuspid regurgitation may cause inadequate pulmonary blood flow and atrial right to left shunting, resulting in the significant neonatal hypoxia and cyanosis as witnessed in the post-natal presentation of our patients.

The increased pressure and pulsatility in the pulmonary artery result in increased mechanical stresses on the pulmonary vasculature and dilatation of the vessels.^{6,18} This stress on the pulmonary valve and sinuses of Valsalva may result in pulmonary stenosis, presumably on very much the same mechanism as the stress (flow-related) on the sinuses causes stenosis in the recipient twin of the twin-to-twin transfusion syndrome.^{19,20} The stress on the sinuses also may lead to further pulmonary valve dilatation, abnormal growth, and development with intensification of existing pulmonary regurgitation. The significant pulmonary regurgitation gives rise to a giant pulse wave, leading to excessive dilatation of the pulmonary arteries, which may cause compression (leading to bronchomalacia) or even obstruction of the bronchi with trapping of the foetal lung fluid (intra-uterine equivalent of post-natal air trapping)—explaining the hyperinflation and microcystic changes noted in the lungs of one of our patients (Figure 4).

Cardiac findings

Excessive RV hypertrophy was seen in all our patients and also seems to be a consistent finding in other reports.¹⁵ The authors

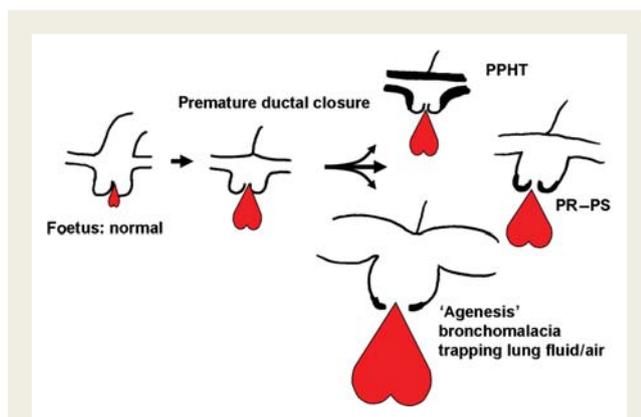


Figure 4 Schematic diagram of possibilities after pre-natal ductal closure: acute increase in pressure in pulmonary trunk with augmented pulmonary valve regurgitation; this may result in medial hypertrophy with 'persistent pulmonary hypertension' (PPHT), or moderate dilation of the sinuses of Valsalva with pulmonary valve dysfunction—pulmonary regurgitation (PR) or stenosis (PS); abnormal growth may lead to 'agenesis' of the pulmonary valve with enormous PR, leading to aneurismal dilatation of the pulmonary trunk and branch arteries with possible compression of airways. See text for details.

hypothesize that this reflects compensatory hypertrophy in response to the dramatically increased afterload. After birth, the sudden drop in afterload leads to 'collapse' of the dilated and hypertrabeculized RV. This would explain the high incidence (75%) of bipartite RV as a post-natal finding.

Nearly all our patients had significant pulmonary regurgitation out of proportion to what is expected at the specific gestational age. The association between premature ductal closure and abnormal pulmonary valve with pulmonary regurgitation is noteworthy. This is more than a co-incidence, since a similar association exists in tetralogy with absent pulmonary valve and absent foetal ductus.^{6,21} This may indicate that there is a direct relationship between foetal closure of the duct and the development of marked pulmonary regurgitation and therefore this may be a marker of the downstream effects of premature ductal closure. Other reports^{3,4,18} have also described the association of right heart failure and hydrops foetalis, as seen in some of our patients with ductal dysfunction.

Outcomes

In our experience, early induction of delivery might be advantageous in patients with premature closure of the duct if right heart dysfunction increases—this has also been advocated in other studies.^{2,3} Early delivery should result in an exponential decrease in pulmonary vascular resistance, thereby unloading the RV. Damage to the pulmonary vasculature due to the high pressure may thus be minimized.

Seven patients were treated with supplemental oxygen only and responded well, indicating mild disease. Five patients required ventilation with pulmonary vasodilators; one was put on ECMO and survived. The mortality rate of 25% caused by pre-natal ductal dysfunction in this study is high. All three deaths were due to severe respiratory failure. Marked right to left shunt via the foramen ovale and RV dysfunction was noted in all three patients. It is therefore clear that post-natal high pulmonary vascular resistance due to premature closure of the ductus arteriosus may pose a grave risk. The difference in outcomes found in this study illustrates the marked variability in clinical presentation and reversibility of effects.

During follow-up, two patients had right heart pathology which needed treatment a considerable time after birth. Interestingly, another patient presented with a cardiomyopathy 4 years later. We therefore suggest that long-term follow-up may be considered in infants where foetal closure of the ductus has been diagnosed.

Causes

The causes of pre-natal closure of the duct are not clear, as a matter of fact, the most frequent 'cause' is spontaneous idiopathic closure.^{4,22} Non-steroidal anti-inflammatory drugs are known to cause ductal constriction if ingested late in pregnancy.^{23–26} This might have been the case in at least two of our patients. One of our patient's mother took an NSAID at 20 weeks of gestation, an age where most literature would state that there is insufficient smooth muscle for the duct to constrict. In one patient, the mother had disulfiram implanted prior to pregnancy. This drug has to date not been reported to be associated with ductal dysfunction.²⁷ It is important to recognize that direct causality could not be proven or disproven in this study.

Study limitations

Apart from being a retrospective analysis, the main limitation is the fact that our institution is a tertiary-care referral centre. Patients referred first need to have an abnormality noticed during routine foetal screening and are as a result already highly selected. Therefore, the true prevalence of ductal dysfunction may be grossly underestimated.

During the study period, we have seen several cases presenting later than 24 h after birth with the clinical presentation of a murmur or cyanosis associated with excessive RV hypertrophy, dilation of right heart structures, and a closed duct—these were not included since we did not have unequivocal proof of pre-natal ductal dysfunction. However, it is our clinical judgement that these findings were most likely due to pre-natal ductal dysfunction. It accentuates the fact that we are dealing with a wide spectrum of degree of pre-natal ductal dysfunction. Only clinically relevant cases will be detected, whereas intermediate variants such as partial constriction of the ductus or transient dysfunction will most likely be missed. Therefore, further research to ascertain the true prevalence and scope of this phenomenon is indicated. The study also illustrates that it is important for the antenatal specialist, when confronted with a cardiovascular lesion, to think ‘upstream’ to detect causes as well as ‘downstream’ to detect the effects.

Conclusion

Foetal premature closure of the arterial duct causes stress at different foetal ages and many different levels of the right heart and pulmonary circulation, resulting in a wide range of secondary pathology. Disproportionate RV hypertrophy, right atrial and ventricular dilation, and moderate to severe tricuspid and pulmonary valve regurgitation are the most frequent ECHO abnormalities. Dysplasia of the pulmonary valve associated with regurgitation may be a marker of foetal ductal dysfunction. Clinical outcomes range from antenatal hydrops to mild, reversible respiratory distress and even neonatal death. Premature induction of delivery might be beneficial in selected cases.

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