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ORIGINAL SCIENTIFIC PAPER

# Dysfunction of the foetal arterial duct results in a wide spectrum of cardiovascular pathology

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**ABSTRACT**

**Objective:** Foetal ductal problems may have various cardiopulmonary consequences. This study aimed to identify the spectrum of ductus arteriosus (DA) dysfunction (closure, constriction, kinking, aneurysm and thrombosis) and the resultant clinical and echocardiographic presentation in foetuses and neonates.

**Methods and results:** This is a retrospective analysis of serial pre- and post-natal data of 27 cases of foetal ductal dysfunction diagnosed at a median gestational age of 33 weeks (range 20–39). The most common abnormalities observed were premature closure of the DA in 56% (15/27) and constriction in 29% (8/27). Right ventricular hypertrophy was present in 75% ($n = 11/15$) of foetuses with premature DA closure, while ventricular dilation (4/7, 57%) was a more common feature in foetuses with ductal constriction. After birth, 63% (17/27) of new borns presented with cyanosis and pulmonary hypertension that required active treatment. Three infants died after birth. Abnormalities resolved spontaneously after birth in about 50% of patients. In some children, pulmonary valve stenosis and regurgitation was progressive and required further treatment.

**Conclusions:** An abnormal right heart on foetal four-chamber ultrasound view should alert the sonographer to the possible presence of foetal ductal dysfunction. Ductal occlusion, transient or fixed constriction, kinking and aneurysm formation are associated with foetal cardiopulmonary sequelae. Symptoms and pathology is probably related to the type, foetal age, rapidity of progression and duration of intrauterine ductal dysfunction. Correspondingly, clinical outcomes vary ranging from little or no symptoms to severe respiratory distress and even foetal or neonatal death.

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## Introduction

The ductus arteriosus (DA) in the foetus is anatomically and functionally quite unlike the post-natal structure. The foetal DA is larger than the aorta and responsible for delivering two thirds of the total combined foetal cardiac output [1]. A core function of the DA is to provide unrestricted blood flow from the right ventricle (RV) to the descending aorta; this allows development of the fragile pulmonary vascular bed while simultaneously letting unhurried parallel development of the intricate structure of the left ventricle take place. A complex balance of constricting and relaxing factors ensures that the DA remains patent throughout foetal life and that the potent mechanisms of ductal closure remain suppressed until birth [2–4]. Patency in the intrauterine environment is maintained by chemical and neurohumoral interactions of which prostaglandins are the most important [5]. Towards the end of gestation, the ductus changes in preparation for post-natal closure and only a third of right ventricular output goes through the duct whilst 24% goes to the lungs [6]. The medial muscle of the duct thickens, endocardial cushions develop and the duct changes in shape: it elongates, angulates and becomes tortuous [7]. It stands to reason that effects on any of these mediators during any stage of foetal life may have a corresponding effect on the developing cardiac structures.

Abnormalities of the foetal DA have been documented in several reports and consist largely of premature closure, constriction (idiopathic and secondary to certain chemicals), elongation, kinking and aneurysm formation [3,8–22]. Reported cardiovascular effects of prenatal ductal abnormalities include excessive right

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ventricular hypertrophy or dilation, tricuspid regurgitation, pulmonary artery dilation, absent pulmonary valve syndrome, hydrops foetalis, intrauterine and postnatal death [23]. Close follow-up and delivery in specialized centres have been recommended in these cases. The overwhelming majority of reports focus on foetal presentation and as a result, preciously little is known regarding the postnatal presentation and outcomes.

Since our institution has an extensive programme of antenatal screening, the aim of this study was to define the progression and morphological abnormalities of the heart in the presence of dysfunction of the foetal DA and to describe the presentation and outcomes in these individuals after birth.

## Patients and methods

This is a retrospective analysis of ante- and post-natal echocardiographic and clinical data. Foetal cardiac databases from 1998 to 2015 were searched: 1602 foetuses were referred in that time period for abnormal cardiovascular findings.

## Inclusion criteria

Foetuses were included if problems such as ductal constriction, closure, excessive elongation and kinking or aneurysm of the DA were observed either as an incidental finding but most frequently as part of a workup of abnormal findings, typically of the right heart. In the latter, only those in whom abnormalities of the DA were the only possible root cause and who had both antenatal and post-natal examinations were included. Congenital heart defects usually associated with abnormalities of the DA such as tetralogy of Fallot, truncus arteriosus, severe pulmonary valve stenosis, etc. at the time of presentation were excluded. Typical examples can be viewed in Figures 1–4.

In all foetuses, a complete foetal echocardiographic examination was carried out by an expert foetal medicine specialist and a paediatric cardiologist. Standard foetal echocardiographic views with several Doppler modes were obtained during routine examination by the foetal ultrasound service. Constriction was considered present if discrete narrowing of a foetal DA was observed on routine three-vessel view in the presence of turbulent flow on colour flow Doppler mapping or if Doppler flow velocity was increased. Kinking was defined as any abnormal shape or angulation of the DA together with the inability to demonstrate the entire ductus in a single plane. Closure was diagnosed when no DA could be demonstrated by Doppler, colour Doppler flow mapping and two-dimensional ultrasound. In order to obtain an accurate assessment of presentation over the study period, eight foetuses which formed part of our previous publication on ductal complete closure, were included [23]. Routine echocardiography was performed soon after birth (within minutes to hours) using standard echocardiographic protocols.

Morphological abnormalities were subjectively classified as mild, moderate or severe depending on the degree of right atrial (RA) and right ventricular dilation (mild $\leq$25%, moderate 25–50%, severe $>$50% larger than left atrium or ventricle (LV), respectively), right ventricular hypertrophy (mild $\leq$25%, moderate 25–50%, severe $>$50% thicker compared to the LV free wall myocardium) or tricuspid regurgitation

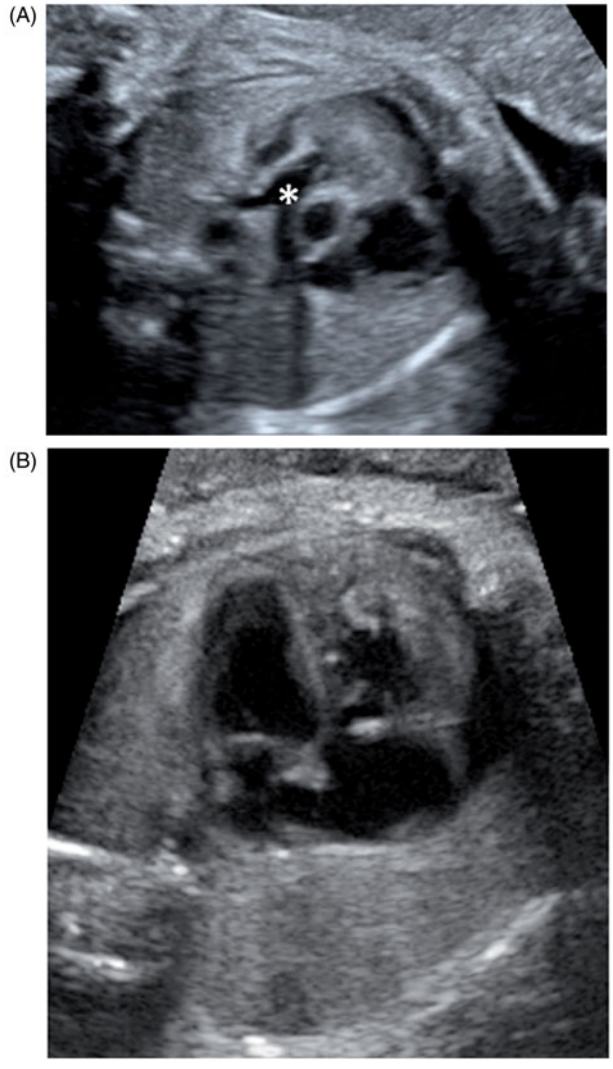


**Figure 1.** Typical foetal ultrasound presentation of DA closure. (A) Premature DA closure (no 16). No DA demonstrated, adult-type appearance of the pulmonary artery bifurcation (*). (B) Foetal four-chamber view of same foetus; note the severely dilated RA, marked RVH (160% of LV free wall).

(colour flow Doppler jet length or width: mild ≤25%, moderate 25–50%, severe >50% of RA) .

Approval from the local medical ethics committee was obtained. Foetal and postnatal echocardiograms were independently reviewed by a paediatric cardiologist and patient records used to gather clinical and demographic information. All abnormalities were noted and data entered into standard spread sheets for analysis. Data are presented as medians with minimum and maximum ranges where appropriate.

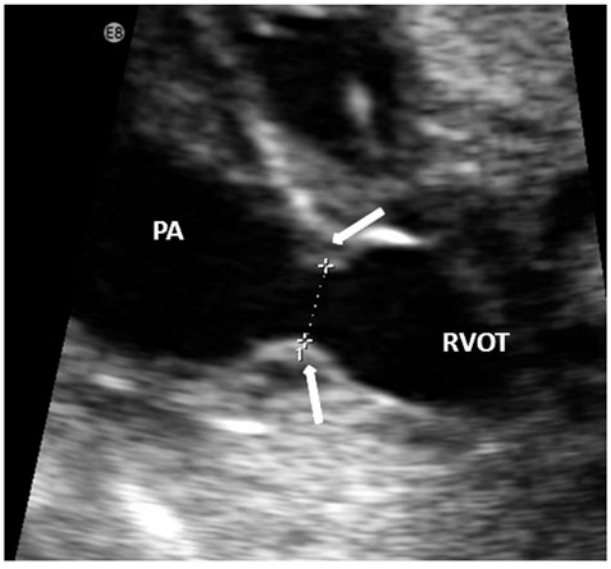


Figure 2. Dilated pulmonary artery. Foetal echocardiogram (no 21) shows huge dilated pulmonary artery PA with 'unguarded' orifice and dysplastic pulmonary valve (arrow). Pulmonary regurgitation was well tolerated after birth and the patient required future right ventricular revalvulation. RVOT-right ventricular outflow tract.

## Results

Twenty-seven ($n = 27$) data sets with complete ante- and post-natal longitudinal data were included. Details can be viewed in Tables 1 and 2.

## Before birth: foetal presentation

Foetal right heart abnormalities assessed for possible DA dysfunction as root cause included asymmetrical cardiac chambers (right atrial (RA) and/or right ventricular (RV) dilation) ($n = 6$), abnormal tricuspid valve regurgitation ($n = 2$), right ventricular hypertrophy (RVH) ($n = 7$), pericardial effusion ($n = 3$), pulmonary artery dilation ($n = 1$). There were seven ($n = 7$) cases in which DA abnormalities were incidentally found during routine antenatal ultrasound examination and one was referred because of maternal anti-inflammatory drug ingestion. History of maternal drug ingestion was present in seven patients: non-steroidal anti-inflammatory drugs (NSAID) ($n = 3$) and analgesics ($n = 4$), mainly paracetamol. Median gestational age at first diagnosis for the foetuses was 33 weeks (range: 20–39). Foetal and neonatal echocardiographic and clinical data for the patients are depicted in Table 1.

## Ultrasonography

The most common ductal abnormalities observed in the foetuses were premature closure of the DA in 56% (15/27) and constriction in 26% (7/27); abnormalities of shape included kinking and ductal aneurysms (Table 2). Right ventricular hypertrophy and tricuspid regurgitation were present in 75% ($n = 11/15$) and 60% ($n = 9/15$) of foetuses with premature DA closure, respectively.

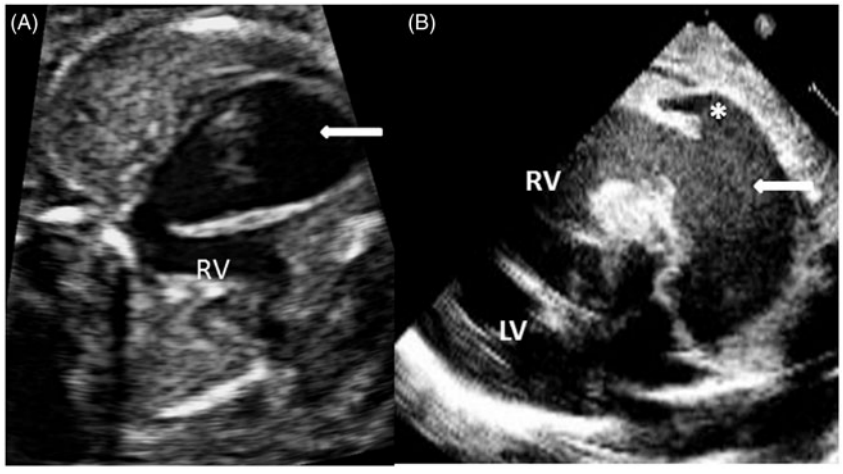


Figure 3. Aneurysm of right ventricle: foetal and neonatal echocardiography. Huge aneurysm of free right ventricular wall (arrow) during antenatal screening in patient no 7. B. Postnatal long-axis view with markedly dilated right ventricle (RV) and pseudoaneurysm (arrow). Left ventricle (LV) small in comparison.

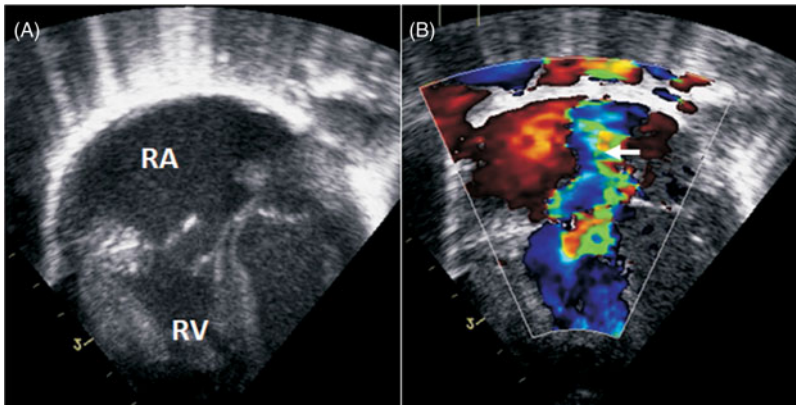


**Figure 4.** Typical postnatal echocardiographic appearance. Typical four-chamber echocardiogram of infant with post-natal presentation of ductal dysfunction in patient no 16. The patient presented with a dilated right atrium and ventricle, pulmonary hypertension and cyanosis. (A) The patient has severe RV hypertrophy (210% LV free wall) with a flail valve due to ruptured chordae (arrow). (B) Severe tricuspid regurgitant jet (blue) can be observed with colour Doppler mapping (arrow).

**Table 1.** Antenatal findings and postnatal outcome.

| | Foetal findings | | | Postnatal presentation | | | | |
|---|---|---|---|---|---|---|---|---|
| | GA | Diagnosis ductal abn | Mat drugs | GA | Delivery | Presentation | Treatment | Inotropes |
| 1 | 34 | Aneurysm | – | 35 | Induction | Asymptomatic | – | – |
| 2 | 39 | Aneurysm | – | 40 | Spontaneous | Asymptomatic | – | – |
| 3 | 32 | Tortuous | – | 39 | Spontaneous | Asymptomatic | – | – |
| 4 | 39 | Tortuous | – | 40 | Induction | Cyanosis | Oxygen | – |
| 5 | 32 | Kinking | Analgesic | 35 | Induction | Cyanosis | CPAP | – |
| 6 | 27 | Constriction | – | 40 | Spontaneous | Asymptomatic | – | – |
| 7 | 26 | Constriction | – | 36 | Induction | Cyanosis | CPAP | – |
| 8 | 28 | Constriction | – | 38 | Induction | Asymptomatic | – | – |
| 9 | 24 | Constriction | Analgesic | 40 | Spontaneous | Asymptomatic | – | – |
| 10 | 25 | Constriction | Analgesic | 37 | Induction | Cyanosis | IPPV HFO NO | Yes |
| 11 | 37 | Constriction | – | 39 | Caesarean section | Cyanosis | Oxygen | – |
| 12 | 32 | Constriction | – | 40 | Spontaneous | Asymptomatic | – | – |
| 13 | 38 | Closed | NSAID | 38 | Caesarean section | Cyanosis | IPPV | Yes |
| 14 | 34 | Closed | – | 40 | Induction | Cyanosis | IPPV NO | Yes |
| 15 | 27 | Closed | – | 29 | Induction | Cyanosis | IPPV HFO NO | Yes |
| 16 | 34 | Closed | – | 35 | Induction | Cyanosis | IPPV NO | Yes |
| 17 | 33 | Closed | – | 34 | Induction | Cyanosis | CPAP | – |
| 18 | 20 | Closed | – | 39 | Spontaneous | Cyanosis | IPPV HFO | Yes |
| 19 | 28 | Closed | – | 37 | Induction | Cyanosis | CPAP | – |
| 20 | 34 | Closed | NSAID | 37 | Induction | Cyanosis | Oxygen | – |
| 21 | 21 | Closed | Analgesic | 39 | Caesarean section | Cyanosis | Oxygen | – |
| 22 | 38 | Closed | – | 38 | Caesarean section | Cyanosis | Oxygen | Yes |
| 23 | 33 | Closed | – | 39 | Spontaneous | Asymptomatic | – | – |
| 24 | 39 | Closed | – | 39 | Induction | Asymptomatic | – | – |
| 25 | 39 | Closed | – | 40 | Spontaneous | Asymptomatic | – | – |
| 26 | 35 | Closed | NSAID | 35 | Induction | Cyanosis | CPAP | – |
| 27 | 36 | Closed | – | 36 | Spontaneous | Cyanosis | CPAP | – |

CPAP: continuous positive airway pressure; GA: gestational age at first presentation and birth; HFO: high-frequency oscillation; IPPV: intermittent positive airway pressure; ma: maternal; NSAID: non-steroidal anti-inflammatory drug; NO: nitrous oxide.

In contrast, right heart dilation appeared to be more common in foetuses with ductal constriction, with right ventricular dilation in 57% (4/7) and right ventricular hypertrophy in only 38% (3/7, 38%) of this group ($p = .034$, 95% CI: 0.69–4.24). Pericardial effusions and right ventricular dysfunction were also observed in some foetuses.

## After birth: neonatal presentation

Premature induction of labour to prevent progression of right heart dysfunction or pulmonary vascular damage was carried out in 52% (14/27) of the mothers at a median gestational age of 36 weeks (range: 29–36). Thirty-seven percent ($n = 10$) of infants were completely asymptomatic immediately after birth. All infants presenting with cyanosis (63%, $n = 17$) required either additional oxygen administration ($n = 5$), nasal continuous positive pressure (CPAP) ($n = 6$) or intermittent positive pressure ventilation (IPPV) ($n = 6$); three required high-frequency oscillation. Ventilatory support was required for a median of 5 days (range: 1–14) in survivors. In four infants, nitric oxide was administered and seven required inotropes including milrinone,

**Table 2.** Antenatal and post-natal echocardiographic findings and outcome.

| | Foetal cardiac findings | | | | | | Post-natal cardiac findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Foetal ultrasound | | | | | Echocardiography | | | | | |
| | Ductal abn | RA | TR | RV dilation | RVH | Other | RA | TR | RV dilation | RVH | Other | Follow-up |
| 1 | Aneurysm | | – | – | – | PS | – | – | – | – | – | Resolved |
| 2 | Aneurysm | – | – | – | – | – | – | – | – | – | Infarction left lung | Resolved |
| 3 | Tortuous | – | – | – | – | Normal | – | – | – | – | – | Resolved |
| 4 | Tortuous | – | – | – | Severe | – | Moderate | Moderate | – | Severe | – | Resolved |
| 5 | Kinking | Moderate | Severe | – | Severe | RV hypocontractility, TiV thickened | Moderate | Mild | – | Severe | – | Resolved |
| 6 | Constriction | – | – | Severe | Moderate | Bipartite RV | – | – | – | Severe | VSD, bipartite RV | Resolved, spontaneous closure VSD |
| 7 | Constriction | – | – | Severe | – | Mild PS, aneurysm RV | – | – | Severe | Severe | Severe PR, RV false aneurysm | PR |
| 8 | Constriction | – | – | – | Severe | Bipartite RV | – | – | – | Severe | Critical PS | PA angioplasty, stent DA |
| 9 | Constriction | – | – | – | – | PA dilation | – | – | – | – | PS | PA angioplasty 3mo |
| 10 | Constriction | Moderate | Severe | Severe | – | Cardiomegaly, pericardial eff | Severe | Severe | Moderate | Severe | unct PA | TiV repair 3w, replacement 5w |
| 11 | Constriction | Severe | Severe | Severe | – | – | Severe | Mild | – | Severe | SVT | Ablation 2mo |
| 12 | Constriction | – | – | – | Severe | RVH | – | – | – | Moderate | MR moderate | Resolved |
| 13 | Closed | – | Moderate | – | Moderate | Pericardial eff | – | Mild | – | Moderate | Pericardial eff | Resolved |
| 14 | Closed | | – | – | Severe | Mild hypoplasia MPA | – | Severe | – | Severe | RVOTO, bipart RV | Demised |
| 15 | Closed | – | Severe | Moderate | – | – | – | – | – | Severe | – | CMP, MiV ring 4y |
| 16 | Closed | Severe | Severe | Moderate | Severe | – | Severe | Severe | Moderate | Severe | funct PA | Demised |
| 17 | Closed | – | – | – | Moderate | – | – | Mild | – | Severe | – | Resolved |
| 18 | Closed | – | Mild | Moderate | Moderate | Microsystic lungs | – | – | Mild | Severe | Air trapping | Demised |
| 19 | Closed | Moderate | Moderate | – | Moderate | PS, PR | Mild | Mild | – | Severe | PS/PR | PuV replacement 2y and 8y |
| 20 | Closed | – | – | – | Moderate | Bipartite RV | – | – | – | Severe | PS | PA angioplasty 7mo, ASD closure 8y |
| 21 | Closed | – | – | Moderate | – | PuV thickened | – | – | Moderate | – | Agenisis PuV | PuV replacement 7y |
| 22 | Closed | – | – | – | Severe | Pericardial eff, RV hypocontractility | – | – | – | Severe | – | Resolved |
| 23 | Closed | Moderate | Severe | – | Severe | – | – | – | – | Severe | – | Resolved |
| 24 | Closed | Moderate | Severe | Moderate | – | Pericardial eff | – | – | – | – | ALTE after 12h | Resolved |
| 25 | Closed | – | – | Severe | Moderate | – | – | Mild | – | Severe | – | Resolved |
| 26 | Closed | – | Severe | Moderate | – | RV hypocontractility | – | – | Mild | – | RV dysfunction | Resolved |
| 27 | Closed | – | Mild | Moderate | Severe | – | – | – | – | Moderate | – | Resolved |

MR: mitral regurgitation; PA; pulmonary atresia; PuV: pulmonary valve; RA: right atrium; RVOTO: right ventricle outflow tract obstruction; TiV: tricuspid valve; TR: tricuspid valve regurgitation, eff: effusion; VSD: ventricular septal defect. Only abnormal findings during echocardiography indicated; empty fields indicate that no abnormality was detected.

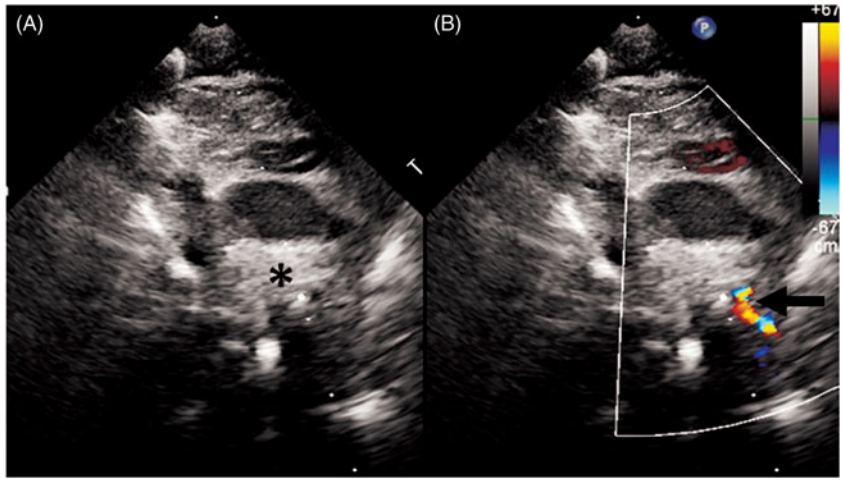


**Figure 5.** Thrombus in pulmonary artery. Echocardiogram of large thrombus in ductus aneurysm and turbulent flow in left pulmonary artery in patient no 2 who presented on day 3 with infarction of left lung. (A) Two-dimensional short axis shows thrombus in main pulmonary artery (asterisk). (B) Colour flow mapping shows turbulent flow in obstructed left pulmonary artery. Right pulmonary artery was unobstructed.

adrenaline, dopamine and dobutamine (Table 1). No patient was put on elective ECMO.

## Postnatal echocardiography

Echocardiography reflected the antenatal findings with moderate-to-severe RVH present in 75% of all infants (20/27) (Table 2). The neonates with prenatally diagnosed DA aneurysms ($n = 2$) were asymptomatic initially, but one developed a thrombus in the aneurysm on day 3. This thrombus extended into the left pulmonary artery and caused infarction of the left lung. It improved following intravenous anticoagulation (Figure 5). Foetus no. 11 with constriction of the DA and a dilated right atrium (RA) presented with a supraventricular tachycardia (SVT) requiring treatment. One infant (no. 25) with closure of the DA was initially asymptomatic but had an acute life-threatening event 12 hours after delivery (transient apnoea and bradycardia). The baby only required further observation in hospital.

Three infants with premature closure of the DA died, two within 24 h:

- The first infant presented with premature DA closure and severe RVH (no. 14), developed cyanosis and severe pulmonary hypertension after birth. The infant was ventilated for 12 days and died 3.6 months later after attempted palliative surgery for right ventricular outflow tract obstruction.
- A second neonate with premature DA closure and RVH (no. 16) died with 'functional pulmonary atresia' within 24 h; partly due to significant tricuspid regurgitation as a result of a flail valve, partly due to very high pulmonary vascular resistance.
- A third neonate who developed prenatal cystic lung malformations (no. 18): the foetus developed aneurysmal dilation of the pulmonary trunk and branch vessels, causing retro-obstructive micro cystic lung disease, which after birth resulted in lethal air trapping (this patient was discussed in detail in the previous publication) [23]. The infant died after 3 h due to respiratory failure.

## Follow-up

Postnatal follow-up varies between 1 month and 16 years (median 11 mo.) (Table 1). In just over half of patients ($n = 15$), the symptoms resolved over time, usually within days to weeks. One child with significant prenatal RVH and flail tricuspid valve presented with persistent severe tricuspid regurgitation after birth. Tricuspid valve repair was attempted at 3 weeks of age but required a surgical valve replacement 2 weeks later. This was subsequently replaced 14 months later by a trimmed Melody valve during a transhepatic procedure. Two patients needed pulmonary valve replacements: one at ages 2 and again at 8 years; the other at the age of 7 years. A further two patients required percutaneous pulmonary valve balloon angioplasty at 3 and 7 months after birth for pulmonary valve stenosis. A foetus who presented with hydrops foetalis (no. 15), developed non-compaction of the left ventricle and cardiomyopathy after birth; a mitral valve ring was surgically inserted 4 years later.

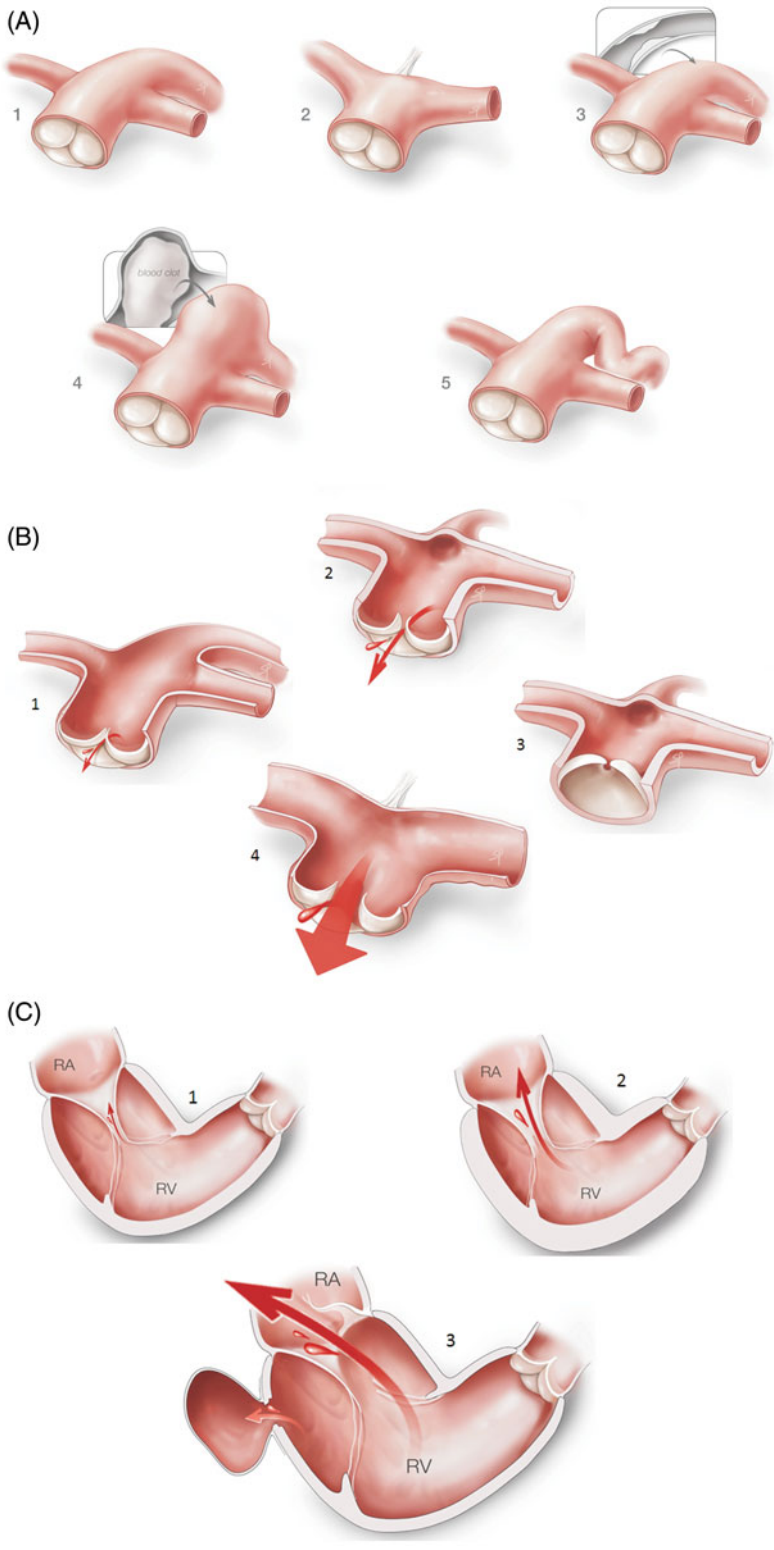


**Figure 6.** Diagrammatic representation of ductal pathology and pathophysiology. (A) *Spectrum of ductal dysfunction:* 1. Normal foetal ductus, similar in size to pulmonary artery. PA – pulmonary artery. 2. Complete ductal closure with adult type of bifurcation. 3. Constriction of ductus – this may be intermittent and transient. 4. Aneurysm of ductus. Thrombus in aneurysm which may extend into the pulmonary arteries, usually the left. 5. Elongated and kinked ductus. (B) *Pulmonary valve abnormalities*: 1. Normal pulmonary artery, minimal pulmonary regurgitation. 2. Pulmonary hypertension; dilated main pulmonary artery and hypertrophy of media with some regurgitation. 3. Pulmonary stenosis – abnormal dysplastic valves due to increased tension on the pulmonary valve sinuses. 4. Pulmonary regurgitation – dilated main pulmonary artery and branches, valves dysplastic and underdeveloped, usually associated with complete ductal closure. (C) *Right ventricular abnormalities.* 1. Normal right ventricle with mild tricuspid valve regurgitation. 2. Dilated and hypertrophied right ventricle with moderate tricuspid regurgitation. 3. Dilated ventricle with high pressure, tear in muscle with resulting aneurysm. Flail tricuspid valve (arrow) with severe regurgitation. Arrow points to aneurysm.

An ablation was performed at the age of two months for the infant who presented with a SVT (no. 11). Two patients with right ventricular outflow tract obstruction remain in follow-up and may require future intervention.

## Discussion

Results of this study provide evidence that a spectrum of DA abnormalities occur in the foetus. This is associated with varying degrees of cardiac and pulmonary consequences both ante- and post-natally. Clinical expression varies from virtually asymptomatic to intrauterine and postnatal demise probably reflecting duration and severity of ductal dysfunction. The serial aspects of this study add to the understanding of the ramifications and postnatal recognition of this little known condition.

Premature closure and constriction were the most common DA abnormalities, occurring in 85% of foetuses in the study. Ductal constriction during foetal life is recognized by calibre mismatch, torsion, turbulent flow and abnormal blood flow velocities [13,17,18]. Although idiopathic forms exist, it is commonly caused by polyphenols in the diet and maternal exposure to drugs, especially drugs that inhibit prostaglandin synthesis, although idiopathic constriction also occurs [13,14,17]. Non-steroidal anti-inflammatory drugs, aminophylline, aspirin, corticosteroids and recently paracetamol have been described to have similar effects on the ductus arteriosus [24–30]. In tortuous and kinked DA, we have observed similar but less pronounced right heart abnormalities. Ductal aneurysms are not uncommon during foetal life and it is probably tolerated and follows a benign course as long as there is no significant flow disturbance, rupture or thrombus formation [18,20,22].

During foetal life, right heart morphological abnormalities, such as RVH, TR, right atrial dilation, pulmonary artery and right ventricular dilation and dysfunction were the most frequent echocardiographic features. Comparable to other reports we observed that right ventricular hypertrophy and tricuspid regurgitation are more prominent in cases of premature DA closure while RV dilation is more common in DA constriction [13,18,20,22]. This may indicate that complete DA closure represents a worse end of the spectrum of DA dysfunction and as a result comes to the physician's attention faster.

Premature induction of labour may prevent further cardiac and/or pulmonary damage and was felt to be the best strategy in some newborns (Table 1). After birth, cyanosis and pulmonary hypertension were the most common presenting symptoms. These infants often required oxygen administration, ventilation, intensive care admission and aggressive treatment of pulmonary hypertension. It should be pointed out that in the absence of prenatal suspicion of premature closure of the DA, in 30% of patients in this series idiopathic persistent pulmonary hypertension of the newborn would probably have been diagnosed, and in 8% bipartite right ventricle. During the study period, we have seen 26 other newborns (not included in this paper) who presented with idiopathic RVH-pulmonary hypertension with foetal ductal dysfunction as most likely aetiology. This is not unexpected in view of the pre-existent intrauterine pulmonary hypertension as a result of ductal problems [31,32]. Therefore, although DA problems appear to be rare, it is most likely underreported since most screening programmes do not include late pregnancy scanning, and less severe and asymptomatic forms will therefore not come to the attention of a clinician.

Ductal problems are potentially lethal as reflected by the 10% mortality in this study, all of which occurred in the premature DA closure group. Follow-up revealed a tendency towards progression of pulmonary regurgitation and stenosis, especially after birth. These effects are difficult to predict since they occurred in all forms and degrees of DA abnormalities. However, they appear to be more frequent when the pulmonary artery was dilated or pulmonary valve leaflets appeared abnormal on antenatal ultrasound. In some children, this required further and multiple interventions in the years during follow-up.

## Postulated presumed pathophysiological events

The authors hypothesize that mechanical obstruction of normal ductal flow induces a number of pathophysiological changes in the right heart: pulmonary artery (PA) hypertension with hypertrophy and dilation, pulmonary valve regurgitation (PR) or stenosis, RV dilation, RVH, tricuspid valve regurgitation and muscular tears with flail-valve and pseudoaneurysm formation (Figure 6) [33]. As a direct consequence, the pulmonary arterial walls and sinuses are submitted to increasingly elevated pressures. More importantly, the fragile and sensitive pulmonary vascular bed is exposed to high pressure. Animal studies have shown that marked medial hypertrophy sets in rapidly, hampering the normal postnatal pulmonary vascular relaxation [34,35]. At the valvar level, the increased pressure and pulsatility in the main pulmonary artery lead to dilation of the vessels and amplify shear

stresses on the valves and sinuses. Increased stress by either pressure or volume have been shown to cause pulmonary valvar stenosis and dysplastic leaflets [36,37]. The combination of increased pressure, decreased run-off, dilatation and abnormal leaflets may lead to pulmonary regurgitation [36]. The pulmonary trunk and branch arteries may become massively dilated and exert secondary compression effects on the airways and surrounding structures similar to foetuses with absent pulmonary valve syndrome [38–40].

The increased afterload on the RV, especially if acute, can lead to right ventricular ischaemia, papillary muscle dysfunction with tricuspid valve regurgitation and muscle tears with flail valve and false aneurysm. In a histopathological study on sheep with induced constriction of the arterial duct, Levin demonstrated ischaemic changes in the myocardium of the right ventricular free wall and papillary muscles [34]. Myocardial necrosis associated with acute increase in pressure provides a reasonable explanation for the unusual finding of a right ventricular pseudoaneurysm in one foetus. It also provides an additional explanation for the high incidence and severity of tricuspid valve regurgitation and foetal death in these foetuses. In contrast, chronic right ventricular hypertension will induce significant hypertrophy; right ventricular dilation is a result of the chronic volume overload due to regurgitation of the tricuspid and pulmonary valves. Eventually, the geometry of the interventricular septum may also become affected, which together with acute left ventricular volume overload, may lead to left heart dysfunction [41].

The severity and cardiopulmonary effects vary widely as demonstrated by the findings of this study. The most plausible explanation can be found considering the nature, degree, rapidity of progression, foetal age of onset and duration of ductal dysfunction. If ductal dysfunction occurs early and is severe, excessive hypertrophy, valve deformation and even death is likely to occur. In milder, transient forms of dysfunction the effects will be limited and the degree of cardiopulmonary abnormalities correspondingly less outspoken. These findings are in agreement with other recent findings [13].

## Recommendations

In the absence of guidelines or specific antenatal treatment careful follow-up of these pregnancies with continuous monitoring should be advised. In selected cases, premature delivery may be indicated, since it is the only effective way to decompress the RV afterload and to avoid secondary changes of intra-uterine pulmonary hypertension [8,42]. Due to the fact that these infants are at high risk of developing respiratory distress, it seems prudent to recommend delivery in a centre providing extensive means of respiratory support and even ECMO. Where symptoms do not resolve spontaneously, these children should be followed-up in the long term.

## Limitations

The descriptive nature and relatively small number imposes study-specific limitations. Evaluation consisted of pre- and post-natal echocardiographic findings. In order to reduce observer bias and variability, all echocardiograms were independently re-examined by a cardiologist. Also, due the retrospective nature and the fact that post-natal data were used as outcome, foetal pulmonary arterial and left heart flows were not recorded. The large number of foetal echocardiograms warrants elucidation. Our hospital is a tertiary referral centre, so there may be an element of selection bias. Belgium has a relaxed policy of antenatal imaging beyond the first and second trimester, and as a result, more antenatal sonars are performed. Ductal pathology typically occurs later in foetal life (second half of pregnancy) which means that this phenomenon is more likely to come to our attention. It should be pointed out that due to the way the study was structured, subtle and asymptomatic forms of DA abnormalities would not have been detected. It would also not give accurate data on the prevalence of dysfunction of the DA. Results of this study highlight the need for further investigation of this phenomenon.

## Conclusions

A broad spectrum of prenatal ductal dysfunction exists. An abnormal right heart on foetal four-chamber view should alert the physician to actively look for signs of foetal DA dysfunction. Ductal occlusion, constriction, kinking and aneurysm formation are associated with cardiopulmonary consequences. Foetal ductal dysfunction leads to cardiopulmonary stress at different foetal ages and many different levels and vary according to the type, severity, foetal age of onset and duration of intrauterine ductal dysfunction. This results in a wide range of secondary pathology dominantly involving the right heart and pulmonary arteries. Correspondingly, clinical outcomes also vary ranging from little or no symptoms to severe respiratory distress and even death. Cyanosis with pulmonary hypertension is the common clinical presentation in

symptomatic individuals. Some right heart abnormalities require long-term follow-up.

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