Foetal ductus arteriosus constriction unrelated to non-steroidal anti-Inflammatory drugs: a case report and literature review

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ABSTRACT
Foetal ductus arteriosus (DA) constriction can be found in complex foetal heart malformations, but rarely as an isolated defect. Although many cases of DA constriction are usually related to Non-steroidal Anti-Inflammatory Drugs (NSAIDs) maternal intake, other causes remain without an established aetiology and are referred to as idiopathic. Recently, a wide range of risks factors or substances (polyphenol-rich foods intake, naphazoline, fluoxetine, caffeine and pesticides) showed a definitive effect upon the pathway of inflammation, causing DA constriction. We report a case of a premature DA constriction in a woman whose possible risk factor was identified in her maternal occupational exposure to solvents and a comprehensive literature review of 176 cases of NSAID-unrelated DA constriction. A 30-year-old Asian woman was referred to our institution at 33 gestational weeks and 0 days because of suspicion of premature DA constriction. The woman had no history of medication intake, including NSAIDs, alcohol, tobacco or polyphenol-rich-food consumption during pregnancy. A detailed foetal echocardiography revealed a normal cardiac anatomy with hypertrophic, hypokinetic and a dilated right ventricle due to right pressure overload, holosystolic tricuspid regurgitation, and, at the level of the DA, high systolic and diastolic velocities, indicating premature ductal restriction. The right outflow showed dilatation of the pulmonary artery with narrow DA. An urgent caesarean section was performed at 33 gestational weeks and 4 days due to worsening of DA PI and signs of right pressure overload, despite the interruption of exposure to solvents. We assume a relationship exists between premature DA constriction and a maternal occupational exposure to solvents. This hypothesis is reinforced by the presence of associated foetal malformations in two of the patient’s children. Further research is needed to confirm the role of exposure to solvents and toxic chemicals in the pathogenesis of DA constriction, also with experimental animal models.

KEY MESSAGES
1. Many cases of DA constriction are usually related to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) maternal intake.
2. A wide range of risks factors or substances (polyphenol-rich foods intake, naphazoline, fluoxetine, caffeine and pesticides) can cause foetal DA constriction.
3. Further investigation are needed to confirm the role of maternal exposure to solvents in the pathogenesis of DA constriction.

Introduction
The ductus arteriosus (DA) is an essential component of foetal circulation. Connecting the pulmonary artery to the descending aorta, it allows 80–85% of the right ventricle output to reach the systemic circulation, bypassing the high resistance fluid-filled lungs [1–4]. This communication between the pulmonary and systemic circulations establishes the parallel circulation in the foetus and equalizes pressure in the right and left ventricle. The patency of DA is maintained during gestation by locally produced and circulating prostaglandins, especially Prostaglandin E2 (PGE2), nitric oxide and low foetal oxygen saturation [5].

With advancing gestation, the DA becomes more sensitive to constricting factors, because it is subject to a progressive vascular remodelling to prepare itself
to postnatal closure [6]. This histological maturation process starts at the second trimester and consists of the thickening of muscular layer [7].

Premature intra-uterine DA constriction could be diagnosed in complex congenital heart malformations, including Tetralogy of Fallot and truncus arteriosus. As an isolated defect, it is usually secondary to the use of medication like NSAIDs, isoxsuprine, fluoxetine and some foods rich in polyphenol like herbal teas, dark chocolate, orange juice, red/purple grapes, berries and coffee [8–12].

The mechanism of NSAID action is inhibition of prostaglandin production by direct constriction of the enzyme cyclooxygenase (COX). Production of prostaglandins is dependent on two enzymes which act in different states, cyclo-oxygenase-1 (COX-1), expressed endogenously, and cyclo-oxygenase-2 (COX-2), locally induced during the inflammatory processes [13]. Both animal and human studies have demonstrated constriction of the ductus after administration of prostaglandin synthetase inhibitors. This effect was not shown to depend on foetal serum concentration of the drug [14,15]. In recent years, also the antiinflammatory and antioxidant effects of foods rich in polyphenol have been demonstrated [16]; these effects are secondary to inhibition of the metabolic route of prostaglandins, especially of COX-2, preventing the transformation of arachidonic acid into prostaglandin [9].

Figure 1. (A) Four chamber view at 33 gestational weeks: hypertrophic and dilated right ventricle, with mild pericardial effusion. (B) Tricuspid valve regurgitation peak velocity (130 cm/s).
Other possible risk factors could be the exposure to solvents or chemicals, but more case confirmations are required [17–18]. Idiopathic premature ductal constriction is considered a rare event.

We describe the case of a premature DA constriction in a woman whose possible risk factor was identified in her maternal occupational exposure to solvents. Moreover, we report, for the first time, a literature review on all cases of DA constriction unrelated to NSAID or congenital heart defects, to investigate the role of others risk factors.

Case presentation

A 30-year-old Asian woman was referred to our institution at 33 gestational weeks and 0 days because of a suspicion of premature DA constriction on a routine third trimester ultrasound. The patient signed a standard written informed consent form for the use of data, pictures, and videos used for teaching and research purposes. This was the third pregnancy. The first newborn was affected by a lip and palate cleft, while the second one was healthy. The current pregnancy had no complications. The woman had no history of medication intake, including NSAIDs, alcohol, tobacco or polyphenol-rich-food consumption during pregnancy. In particular, in order to quantify the polyphenol ingestion, a food frequency questionnaire for consumption of polyphenol-rich foods in pregnant women was performed [19–20]. The total dietary amount of flavonoids was calculated from the USDA Database for the Flavonoid Content of Selected Foods [21], considering the 27 items with higher concentrations of polyphenols higher than 30 mg/100 g of food (green and black tea, mate tea, grape derivatives, dark chocolate, orange juice, fruit teas, olive oil, soy beans, berries, tomato, apples, spinach, and others) as reported by Zielinsky et al. [22]. On the other hand, her occupational exposure to solvents and toxic chemicals, as a hairdresser, (especially cosmetic products) resulted from the maternal and paternal history. A detailed foetal echocardiography revealed a normal cardiac anatomy with hypertrophic, hypokinetic and dilated right ventricle due to right pressure overload. The effects of premature DA constriction (mild pericardial effusion and a dilated and poorly functioning right ventricle) can be seen in Figure 1. The colour and pulsed Doppler interrogation showed holosystolic tricuspid regurgitation (130 cm/s) (Figure 1(B)) with jet that reached the roof of the atrium and at the level of the DA showed high systolic (200 cm/s) and diastolic (80 cm/s) velocities with a reduction in the pulsatility index (PI) (0.8), indicating premature ductal restriction. The right outflow showed dilatation of the pulmonary artery with narrow DA (Figure 2(B)). After the administration of corticosteroids, an urgent caesarean section was performed at 33 gestational weeks and 4 days due to worsening of DA PI and signs of right pressure overload, despite the interruption of exposure to solvents. A 2250 g-male neonate born with Apgar score of 5 and 9 at 1 and 5 min respectively. Post-natal echocardiography revealed an anatomically normal heart with progressive improvement of hypertrophy and right ventricular dilatation.

The newborn was treated immediately after birth with PGE infusion with the aim of reducing the pressure overload of the right ventricle and pulmonary hypertension. This use of prostaglandins is off-label, but free from major side effects. Due to poor response to PGE treatment, it was stopped after 18 h, and therapy with inotropic agents (dopamine) and nitric oxide was initiated to reduce the pulmonary pressure.

Figure 2. Two-dimensional echocardiography, showing ductus arteriosus constriction (arrow). (A) Right outflow tract. (B) Ductal arch view. (C) three-vessel view.
Closure of DA took place 30 h after birth. Collaterally, congenital cataract was found. Normal human karyotype was found in the newborn.

**Methods: comprehensive review of the literature**

The electronic medical database Medline/PubMed was used for research, combining the following terms: foetal ductus arteriosus constriction (472 articles). Titles and abstracts of these articles were screened for relevance by authors to determine which articles were to undergo full-text review (human cases of prenatal DA constriction/closure no NSAIDs or CHD induced). Animal cases of prenatal ductus arteriosus constriction, cases of NSAID related DA constriction, or related to heart defects were excluded (Figure 3). Articles identified at this stage as potentially relevant moved into full text review (Figure 3). The bibliographies of included studies were reviewed to identify additional publications not found through the database search.

**Results**

To date, 176 cases of NSAID-unrelated (and congenital heart defects- unrelated, CHD) premature DA constriction have been reported in the English language literature (from 1946 to 2020).

Including the present report, there are 177 cases of NSAID-unrelated (and not related to heart disease) [4,8,23–54] (Table 1).

Figure 4 report the distribution of etiopathogenesis of human cases in literature no NSAIDs or CHD induced; of the 177 cases found 96 were idiopathic (54.2%), 58 were related to polyphenol rich-food, 5 to paracetamol, 4 were related to genetic arteriopathy (Alagille and Williams Syndrome), 4 cases were related to sympatomimetics drugs, 4 to corticosteroids, 4 to miscellaneous causes, 1 to SSRI consumption and 1 case to lithium consumption. In the literature, many cases are considered as idiopathic, but no one reported about maternal employment. However, it would be important to investigate whether there is a common pathogenetic mechanism form in many cases, such as occupational exposure to solvents or intake of paracetamol (acetaminophen), a drug considered safe in pregnancy. In particular, a repeated dose intake, especially in the third trimester of pregnancy, can have a vasoconstrictive effect [55].

**Discussion**

Patient history was accurately reviewed to identify a possible causative agent. The woman had no chronic illness and was not a smoker. The foetus’s heart had no congenital defects. We asked about medications (especially NSAIDs) and polyphenol-rich foods intake. The mother denied the consumption of any kind of medicine, herbal tea, grapes or other polyphenol-rich food during pregnancy. A dietary intervention for maternal restriction of polyphenol-rich foods or suspension of NSAIDs consumption in the third trimester of pregnancy is accompanied by increase in plasma levels of PGE2 and reversal of foetal ductal constriction [10,27,39,56,57].

In the absence of the most common aetiologies, the occupational exposure to solvents or an idiopathic premature constriction of DA was suggested. The
| Authors (Y) | Sample size | N | Study design | MA (y) | Causative agent (Substance exposure/idopathic) | Dominant echo findings | GA at diagnosis (W) | Treatment | Delivery | GA at birth (w) | Postnatal presentation | Postnatal treatment and course |
|------------|-------------|---|--------------|--------|-----------------------------------------------|------------------------|-------------------|-----------|---------|----------------|-------------------------|-----------------------------|
| Battistoni et al. (the present report) | 1 | 1 | Case report | 30 | Solvents and toxic chemicals | RV dilatation, PA dilatation, narrowed DA, PI on DA, TR, pericardial effusion | 33 | CS after corticosteroids | Immediate CS after corticosteroids | 34 | Progressive improvement of hypertrophy and right ventricular dilatation | Normalized heart | Uneventful. Congenital cataract was found |
| Enzesberger et al. 2012 [23] | 3 | 2 | Case series | 29 | Idiopathic | TR, RA dilatation, constricted DA, PSV,PDV and PI on DA, negative a wave DA, Cardiomegaly, RH hypertrophy, TR, PSV,PDV and PI on DA, negative a wave DA | 33 | Daily FU | CS (maternal request) | 38 | A, Hypertrophic RV | Discharged d 4 |
| | 3 | 29 | Idiopathic | RV dilatation, PSV,PDV and PI on DA, negative a wave DV | 34 | Daily FU | CS (breed- RH function) | 35 | A, RV hypertrophy, TR | Discharged d 5 |
| | 4 | 26 | Idiopathic | RV hypertrophy, PSV,PDV and PI on DA, tortuous S-shaped DA | 34 | CS | CS (non-reassuring stress test) | 36 | A | Oxygen by nasal cannula | Discharged d 15 |
| Genovese et al.2015 [4] | 1 | 5 | Case report | 38 | Paracetamol | RV hypertrophy, PSV,PDV and PI on DA, negative a wave DV | 34 | CS after corticosteroids | Elective CS | 35 | RDS, Marked RV hypertrophy with impaired function, little and tortuous DA | Normal heart 3m |
| Lopes et al 2015 [8] | 16 | 6 | Retrospective analysis | 16–43 | Idiopathic | RV dilatation, severe TR, PSV,PDV and PI on DA | 29 | FU | ND | ND | A | Uneventful |
| | 7 | 16–43 | Idiopathic | RV dilatation, mild TR | 34 | FU | ND | ND | A | Uneventful |
| | 8 | 16–43 | Idiopathic | RV dilatation, mild TR | 32 | FU | ND | ND | A | Uneventful |
| | 9 | 16–43 | Idiopathic | RV dilatation and akiine, severe TR, pericardial effusion, PSV,PDV and PI on DA | 37 | Immediate delivery | ND | ND | Severe PH, severe RV dysfunction | Normal heart 3m |
| | 10 | 16–43 | Idiopathic | RV dilatation, mild TR | 34 | FU | ND | ND | A | Uneventful |
| | 11 | 16–43 | Idiopathic | RV dilatation, severe TR | 36 | FU | ND | ND | A | Uneventful |
| | 12 | 16–43 | Idiopathic | RV dilatation, mild TR | 35 | FU | ND | ND | A | Uneventful |
| | 13 | 16–43 | Idiopathic | RV dilatation, mild TR | 28 | FU | ND | ND | A | Uneventful |
| | 14 | 16–43 | Naphazoline (abusive use of nasal drops) | Mild TR, PSV,PDV and PI on DA | 38 | FU | ND | ND | A | Uneventful |
| | 15 | 16–43 | Asthma attack after pest control (unknown pesticide with bronchodilators) | RV dilatation, severe TR, PSV,PDV and PI on DA | 33 | FU | CS for persistent DA constriction | 37 | PH | Normal heart 15 d |
| | 16 | 16–43 | Naphazoline (abusive use of nasal drops) | RV dilatation, moderate TR, PSV,PDV and PI on DA | 34 | FU | ND | ND | A | Uneventful |
| | 17 | 16–43 | Caffeine (abusive ingestion of cola soft drink, 3–4 l/d) | RV dilatation, moderate TR, PSV,PDV and PI on DA | 31 | FU | ND | ND | A | Uneventful |
| | 18 | 16–43 | Fluoxetine 60mg/d (since beginning of pregnancy) | RV dilatation, moderate TR, PSV,PDV and PI on DA | 28 | FU | ND | ND | A | Uneventful |
| | 19 | 16–43 | Caffeine (abusive ingestion of cola soft drink) | RV dilatation, PI on DA | 33 | FU | ND | ND | A | Uneventful |
| | 20 | 16–43 | Oxymetazoline + Naphazoline (abusive use of nasal drops) | RV dilatation, PI on DA | 34 | FU | ND | ND | A | Uneventful |
| | 21 | 16–43 | Caffeine (abusive ingestion of cola soft drink) | RV dilatation, PI on DA | 30 | FU | ND | ND | A | Uneventful |
| Authors (Y) | Sample size | N | Study design | MA (y) | Causative agent (Substance exposure/idiopathic) | Dominant echo findings | GA at diagnosis (W) | Treatment | Delivery | GA at birth (w) | Postnatal presentation | Postnatal treatment and course |
|------------|-------------|---|--------------|--------|-----------------------------------------------|------------------------|---------------------|-----------|----------|---------------|------------------------|-------------------------------|
| Trevett et al. 2004 [24] | 1 | 22 | Case report | 34 | Idiopathic | Moderate RV hypertrophy, mild TR, $|$ PSV and $|$ Pi on DA, tortuous S-shaped DA | 33 | Weekly FU | Induction for GDM, VD | 38 | A, Normal heart | Discharged d 3 |
| Rakha S. 2017 [10] | 1 | 23 | Case report | 23 | Orange intake (up to 2 kg/d) | RH dilatation, PSV,PDV and $|$ Pi on DA, narrowed DA | 31 | Stop orange intake + FU | Spontaneous VD | 39 | A, Normal heart | Uneventful |
| Okada et al 2018 [25] | 1 | 24 | Case report | 27 | Idiopathic | LV and RA dilatation, severe TR, hypertrophic RV, narrowed DA, no blood flow on DA | 37 | CS | Emergency CS (sinusoidal pattern on CTG) | 37 | Severe dyspnea, dilated cardiomyopathy | Respiratory support (intubation), inotropes and diuretic administration. Discharged d 47, Resolution of cardiomyopathy 6 m |
| Shima et al. 2010 [26] | 1 | 25 | Case report | 27 | Idiopathic | RA dilatation, severe TR, hypertrophic RV, narrowed DA, pericardial effusion | 38 | CS | Emergency CS | 38 | Tachypnea, RA dilatation, massive TR, hypertrophic RV, mild pericardial effusion, Oxygen | Uneventful |
| Vian et al. 2018 [27] | 35 | 26–60 | Case-control | ND | Idiopathic | $|$ PSV,PDV and $|$ Pi on DA, narrowed DA,TR RV hypertrophy, PA retrograde flow, $|$ PSV,PDV and $|$ Pi on DA | ≥28 | Polyphenol-rich food restriction | ND | ND | ND | A, Normal-sized heart | Uneventful |
| Yaman et al. 1999 [28] | 1 | 61 | Case report | ND | Idiopathic | RV hypertrophy, $|$ PSV,PDV and $|$ Pi on DA, TR, mild pericardial effusion, narrowed DA | 39 | Stop steroids | CS for placenta Previa | 38 | A, Normal-sized heart | Uneventful |
| Azancot-Benisty et al. 1995 [29] | 1 | 62 | Case report | 38 | Betamethasone (four courses ) | No flow through DA, no narrowing of DA, RH dilatation, RV hypertrophy, severe TR, negative a wave on DV | 38 | CS | Emergency CS | 38 | A, mild TR, moderate PH, cardiomegaly, RV hypertrophy, closed DA, dyspnea, PH, severe TR with rupture of the anterior papillary muscle, RV hypertrophy | Uneventful Discharged d 3 Normal heart d 14 |
| Wei S. et al. 2011 [30] | 1 | 63 | Case report | 28 | Idiopathic | Cardiomegaly, dilatation of pulmonary trunk, $|$ PSV,PDV and $|$ Pi on DA, moderate TR, narrowed DA | 38 | CS | Emergency CS | 38 | A, DA closed, dilated RV, mild TR, PR | Oxygen, CPAP, inotropes and diuretics, NO (until d 7) |
| Inatomi et al. 2017 [31] | 1 | 64 | Case report | 38 | Idiopathic | Cardiomegaly, dilatation of pulmonary trunk, $|$ PSV,PDV and $|$ Pi on DA, moderate TR, narrowed DA | 36 | CS | Emergency CS (progression to hydrops) | 36 | Oxygen, CPAP, inotropes and diuretics, NO (until d 7) | Uneventful |
| Sridharan et al. 2009 [32] | 2 | 65 | Case report | 34 | Camomile tea | $|$ PSV,PDV and $|$ Pi on DA, narrowed DA | 20 | Stop tea | ND | ND | ND | A, DA closed, dilated RV, mild TR, PR | Uneventful |
|  | 66 | 32 | Case report | 34 | Camomile tea | RV dilatation and poorly contractile, moderate TR and PR, $|$ PSV,PDV and $|$ Pi on DA, narrowed DA | 35 | CS | Immediate CS | 35 | A, DA closed, dilated RV, mild TR, PR | Uneventful |
| Hayes 2016 [33] | 1 | 67 | Case report | 33 | Bio-Oil® (x2/d from II trim) | RA dilatation, hypertrophic and poorly contractile RV, moderate TR, pericardial effusion, $|$ PSV,PDV and $|$ Pi on DA, narrowed DA, negative a wave on DV | 37 | CS | Immediate CS | 37 | Dyspnea, cardiomegaly, PH, RV systolic dysfunction, TR | Oxygen Discharged d 6. Normal heart 6 m |

(continued)
| Authors (Y)          | Sample size | N     | Study design | MA (y) | Causative agent (Substance exposure/idiopathic) | Dominant echo findings | GA at diagnosis (W) | Treatment                  | Delivery          | GA at birth (w) | Postnatal presentation | Postnatal treatment and course |
|---------------------|-------------|-------|--------------|--------|-----------------------------------------------|------------------------|---------------------|-----------------------|-----------------|----------------|----------------------|--------------------------------|
| Srinivasan et al. 2018 [34] | 4           | 68-71 | Case series  | 20-34  | ALGS/WS                                       | RV hypertrophy and dilatation, ↑ PSV, PDA and ↓ PI on DA, TR, narrowed DA | 21–36               | Follow up            | Induction/CS (non-reassuring CTG) | 32–36 | Oxygen up to 6 m. Normal heart 6 m, bur PPS persisted. Oxygen up to 6 d. Cardiomyopathy regression at 2 m. | Dyspnoea, PH, RV hypertrophy, ↑ flow velocities on peripheral PA |
| Schierz et al. 2018 [35]     | 1           | 72    | Case report  | ND     | Paracetamol (3g/d four 4 d in the III trimester), polyphenol-rich foods | ND                    | 38                  | CS                    | Emergency CS       | 38              | Oxygen for 48h. Discharged d 9. Normal heart at 7 w. Oxygen for 36h Antibiotics (sepsis). Discharged d 9. | Dyspnoea, PH, closed DA, RV hypertrophy and dilatation. Dyspnoea, closed DA, RV hypertrophy and dilatation. Hyperechoic RV endocardium and papillary muscle. |
| Hofstadler et al. 1995 [36]  | 4           | 73    | Case report  | ND     | Idiopathic                                    | RV hypertrophy and dysfunction, TR, PR | 37                  | Induction            | CS                    | 37              |                         | Dyspnoea, PH, closed DA, RV hypertrophy and dilatation, TR Hyperechoic RV endocardium and papillary muscle. Oxygen for 14h. Discharged d 6. At 3 m uncomplete regression of RV hypertrophy, but baby is clinically well. Discharged d 8. At 5w uncomplete regression of RV hypertrophy, but baby asymptomatic. Normal RV function, with mild residual RV hypertrophy at 3 w Oxygen with mechanical ventilator. Discharged d 12 Normal heart at 7 m. | |
| 75                   | ND          | 6-days course antibiotics and phenyldimethylpyrazolam, glucocorticoids and ß-blocker | Closed DA, RV hypertrophy and dysfunction, ascites, TR, abnormal umbilical vein pulsations, PA regurgitation | 38                  | CS                    | Emergency CS       | 38              | Dyspnoea, PH, closed DA, RV hypertrophy and dilatation, TR Hyperechoic RV endocardium and papillary muscle. Oxygen for 14h. Discharged d 6. At 3 m uncomplete regression of RV hypertrophy, but baby is clinically well. Discharged d 8. At 5w uncomplete regression of RV hypertrophy, but baby asymptomatic. Normal RV function, with mild residual RV hypertrophy at 3 w Oxygen with mechanical ventilator. Discharged d 12 Normal heart at 7 m. | |
| 76                   | ND          | Bethametasone single course | RV hypertrophy and dysfunction, TR, PA regurgitation | 34                  | Induction            | VD                  | 35              | Closed DA, RV hypertrophy and dilatation, mild TR | | |
| Soslow et al. 2008 [37]     | 1           | 77    | Case report  | ND     | Bethametasone single course                    | Restrictted DA, RV hypertrophy and dysfunction, TR, Abdominal meconium pseudocyst. RV hypertrophy, RA dilatation, tortuous S-shaped DA, no flow on DA, mild TR | 31                  | Weekly FU            | Emergency CS (worsening of RV function) | 32              | Closed DA, RV hypertrophy and dilatation, mild TR | Dyspnoea, closed DA, RV hypertrophy, mild TR Oxygen with mechanical ventilator. Discharged d 12 Normal heart at 7 m. | |
| Choi et al. 2013 [38]       | 1           | 78    | Case report  | 22     | Idiopathic                                    | RV hypertrophy, RA dilatation, tortuous S-shaped DA, no flow on DA, mild TR | 33                  | Induction            | VD                    | 34              | Dyspnoea, closed DA, RV hypertrophy, mild TR Oxygen with mechanical ventilator. Discharged d 12 Normal heart at 7 m. | |
| Zielinsky et al. 2012 [39]  | 51          | 79-129| Case-control | 28 ± 6.5| Polyphenol rich foods                         | ↑ PSV, PDA and ↓ PI on DA, turbulent flow on DA, TR, RV hypertrophy, ↑ PDA, ↓ PI on DA, S-shaped DA, severe TR, RA and RV dilatation, transient PR | 32 ± 3              | Polyphenol-rich food restriction and FU after 3w FU | Spontaneous delivery | ND              | A, normal sized heart | Uneventful |
| Mielke et al. 1995 [40]     | 1           | 130   | Case report  | 28     | Idiopathic                                    | ↑ PSV, PDA and ↓ PI on DA, S-shaped DA, severe TR, RA and RV dilatation, transient PR | 32                  | CS (↑ tricuspid valve insufficiency) | 36              | Closed DA, RV hypertrophy and dilatation, mild TR | Progressive normal heart in the following d. | |

(continued)
| Authors (Y)                  | Sample size | N | Study design   | MA (y) | Causative agent (Substance exposure/idioopathic) | Dominant echo findings                                                                 | GA at diagnosis (W) | Treatment                                                                 | Delivery            | GA at birth (w) | Postnatal presentation | Postnatal treatment and course |
|-----------------------------|-------------|---|----------------|--------|------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------|---------------------------------------------------------------------------|---------------------|--------------------|------------------------|---------------------------------|
| Ishida et al. 2011 [41]     | 1           | 131| Case report    | 29     | Idiopathic                                     | PSV, PDV and PI on DA, mild TR, RH dilatation, PR, hydrops                               | 32                  | CS                                                                         | Emergency CS       | 32                 | closed DA, dyspnea, RV hypertrophy and dilatation, mild TR              | Oxygen intubation, Catecholamine, Discharged d 31, Normal heart 2 m |
| Mielke et al. 1996 [42]     | 1           | 132| Case report    | 34     | Idiopathic                                     | PSV and PI on DA, narrowed DA, RA dilatation, foetal atrial flutter                      | 31                  | Weekly FU, digoxin + verapamil to obtain cardioversion                     | Spontaneous        | 39                 | RV hypertrophy, RA dilatation                                         | Normal heart 3 m    |
| Gewillig et al. 2017 [43]   | 19          | 133| Case series    | ND     | Idiopathic                                     | PSV and PDV, PI on DA, narrowed DA, severe RV dilatation and hypertrophy                | 27                  | FU                                                                         | Spontaneous        | 40                 | A, severe RV hypertrophy                                              | Resolved                        |
|                            |             | 134|                | ND     | Idiopathic                                     | PSV and PDV, PI on DA, narrowed DA, severe RV dilatation and hypertrophy                | 26                  | FU, Induction (RH dysfunction)                                            | VD                  | 36                 | Cyanosis, severe RV hypertrophy and dilatation, A, severe RV hypertrophy, critical Pulmonary stenosis | CPAP                              |
|                            |             | 135|                | ND     | Idiopathic                                     | PSV, and PDV, PI on DA, narrowed DA, severe RV hypertrophy                              | 28                  | FU, Induction (progression RH dysfunction)                                | VD                  | 38                 | Cyanosis, PH, severe TR, moderate RV hypertrophy, RA dilatation, Cyanosis, SVT, mild TR, severe RV hypertrophy, RA dilatation | Oxygen, Ablation 2 m    |
|                            |             | 136|                | ND     | Paracetamol                                    | PSV, and PDV, PI on DA, Pulmonary atresia dilatation                                  | 24                  | FU                                                                         | Spontaneous        | 40                 | A, Pulmonary stenosis, Cyanosis, PH, severe TR, moderate RV hypertrophy, RA dilatation | Pulmonary atresia angioplasty |
|                            |             | 137|                | ND     | Paracetamol                                    | PSV, and PDV, PI on DA, narrowed DA, severe TR, pericardial effusion                   | 25                  | FU, Induction (progression RH dysfunction)                                | VD                  | 37                 | Cyanosis, PH, severe TR, moderate RV hypertrophy, RA dilatation, Cyanosis, SVT, mild TR, severe RV hypertrophy, RA dilatation | IPPV, NO, Inotropes, Tincup valve repair at 3 w |
|                            |             | 138|                | ND     | Idiopathic                                     | PSV, and PDV, PI on DA, narrowed DA, severe TR, severe RH dilatation                   | 37                  | FU                                                                         | CS                  | 39                 | Cyanosis, SVT, mild TR, severe RV hypertrophy, RA dilatation            | Oxygen, Ablation 2 m    |
|                            |             | 139|                | ND     | Idiopathic                                     | PSV, and PDV, PI on DA, severe RV hypertrophy                                        | 32                  | FU                                                                         | Spontaneous        | 40                 | A, moderate RV hypertrophy                                              | Resolved                        |
|                            |             | 140|                | ND     | Idiopathic                                     | PSV, and PDV, PI on DA, no flow DA, severe RV hypertrophy                              | 34                  | FU                                                                         | VD                  | 40                 | Cyanosis, PH, severe TR, severe RV hypertrophy, RVOTO                   | IPPV, NO, Inotropes, death 3 m after attempted palliative surgery of RVOTO |
|                            |             | 141|                | ND     | Idiopathic                                     | PSV, and PDV, PI on DA, no flow DA, severe TR, moderate RV dilatation                  | 27                  | FU, Induction (RH dysfunction with hydrops)                              | VD                  | 29                 | Cyanosis, PH, severe RV hypertrophy, cyanodystrophy                    | IPPV, NO, Inotropes, mitral valve ring a 4 y |
|                            |             | 142|                | ND     | Idiopathic                                     | PSV, and PDV, PI on DA, no flow DA, severe TR, moderate RH dilatation, severe RV hypertrophy | 34                  | FU, Induction for progression RH dysfunction                             | VD                  | 35                 | Cyanosis, PH, severe TR, moderate RH dilatation, severe RV hypertrophy, functional PuV atresia | IPPV, NO, Inotropes, death on day 1 due to high pulmonary vascular resistance |
| Authors (Y) | Sample size | N | Study design | MA (y) | Causative agent (Substance exposure/idopathic) | Dominant echo findings | GA at diagnosis (W) | Treatment | Delivery | GA at birth (w) | Postnatal presentation | Postnatal treatment and course |
|------------|-------------|---|--------------|--------|-----------------------------------------------|------------------------|---------------------|-----------|----------|----------------|-------------------------|--------------------------------|
| Babaoğlu et al. 2013 [44] | 1 | 152 | Case report | 29 | Idiopathic | | | | | | | |
| Becker et al. 1977 [45] | 2 | 153 | Case report | ND | Idiopathic | | | | | | | |
| Becker et al. 1977 [45] | 2 | 154 | Case report | ND | Idiopathic | | | | | | | |
| Authors (Y)               | Sample size | N  | Study design | MA (y) | Causative agent (Substance exposure/idiopathic) | Dominant echo findings | GA at diagnosis (W) | Treatment | Delivery | GA at birth (w) | Postnatal presentation | Postnatal treatment and course |
|--------------------------|-------------|----|--------------|--------|------------------------------------------------|------------------------|---------------------|-----------|----------|----------------|------------------------|--------------------------------|
| Leal et al. 1997 [46]    | 3           | 155| Case series  | 28–38  | Idiopathic                                      | No flow on DA, RV dilatation, mild TR, mild PuV insufficiency | 32                  | ND        | CS       | ND             | A, absent DA flow, RV dilatation | Uneventful, Normal-sized heart on follow up |
|                          | 156         | 28–38| Idiopathic   |        | No flow on DA, RV dilatation, mild TR, mild PuV insufficiency | 41                  | ND        | CS       | ND             | A, absent DA flow, RV dilatation | Uneventful, Normal-sized heart on follow up |
|                          | 157         | 28–38| Idiopathic   |        | No flow on DA, RV dilatation, mild TR, mild PuV insufficiency | 40                  | ND        | CS       | ND             | A, absent DA flow, RV dilatation | Uneventful, Normal-sized heart on follow up |
| Talemal et al. 2016 [47] | 1           | 158| Case report  | 31     | Dexamethasone (1w) for suspected myocardial inflammation in anti-SSA-exposed foetus | PSV, PDV, PI on DA, narrowed DA, mild RH dilatation, mild TR, hyperechogenic Mitral valve | 28                  | Follow up | Spontaneous VD | 38             | RDS, RH dilatation, RV dysfunction, no myocardial inflammation | Uneventful, Endotracheal intubation for 24h, normal heart at 2w. |
| Eidem et al. 2000 [48]   | 1           | 159| Case report  | 35     | Idiopathic                                      | Narrowed DA          | 23                  | FU        | Induced VD | 38             | A, constricted DA | Uneventful |
| Corti et al. 2020 [49]   | 1           | 160| Case report  | 35     | Sertraline (2.5mg/d) Lorazepam (10drops/d) Paracetamol (2-4g/d first trimester and 1-2 g occasionally in the third trimester) Idiopathic | No flow on DA, severe RH dilatation, TR, PuV insufficiency, decreased function of RV, Negative a-wave on DV, PSV, and PDV on DA, narrowed DA, mild RH dilatation, mild TR, RV hyperechogenicity, mild pericardial effusion | 33                  | CS after single course of corticosteroids | CS          | 33             | Dyspnoea, PH, No DA, RV hypertrophy and dilatation, mild PuV insufficiency | Oxygen by nasal cannula, Normal heart 1m. |
| Kim et al. 2003 [50]     | 1           | 161| Case report  | 35     | Lithium (throughout pregnancy) Rh dilatation     | 18                  | FU        | Preterm delivery | ND          | A, mild TR, mild RV hypertrophy and hypococontractility, totally closed DA | Dyspnoea, severe RV dilatation and hypertrophy, severe TR, Closed DA, PH | Uneventful, Progressive normal heart, Discharged 5w. |
| Ellis et al. 2013 [51]   | 1           | 162| Case report  | ND     | Paracetamol (for 7 d after 34 w)                 | 37                  | Induction | VD        | 37             | A, absent DA, RV dilatation, mild TR, mild TR | Mechanic ventilation for 2d, Discharged d 10, Normal heart at 1m. |
| Becquet et al. 2018 [52] | 1           | 163| Case series  | 31     | Idiopathic                                      | PSV, PDV and PI on DA, narrowed DA, mild RH dilatation, mild TR | 32                  | FU        | CS (worsening RV dysfunction) | 38             | Mechanic ventilation for 2d | Uneventful |
| Chugh et al. 2020 [53]   | 1           | 164| Case series  | 31     | Idiopathic                                      | PSV, PDV and PI on DA, narrowed DA, S-shaped DA, mild TR | 33                  | FU        | ND       | ND             | CS | Uneventful |
| Luchese et al. 2003 [54] | 13          | 165| Retrospective analysis | 19 | Idiopathic                                      | PSV, PDV and PI on DA, RH dilatation, hypertrophic RV, mild PR | 33                  | FU        | ND       | ND             | PH | ND |
|                          | 166         | 32 | Idiopathic   |        | PSV, PDV and PI on DA, dilated/hypococontractile RV, mild TR | 27                  | FU        | ND       | ND             | PH | ND |
|                          | 167         | 17 | Idiopathic   |        | PSV, PDV and PI on DA, dilated RH and PA, mild TR | 37                  | FU        | ND       | ND             | A | Uneventful |
|                          | 168         | 35 | Idiopathic   |        | No flow on DA, dilated RH and PA, severe TR and PR, hypertrophic RV | 36                  | FU        | ND       | ND             | Uneventful |
|                          | 169         | 21 | Idiopathic   |        | PSV and PI on DA, mild RV dilatation, mild TR | 34                  | FU        | ND       | ND             | Uneventful |

(continued)
Occupation of both parents as hairdressers, which involved the daily use of organic solvents, could be suspected. Widely discussed in the literature is the association between maternal occupational exposure to solvents (as in hairdressing and cosmetology) and an increased risk of adverse obstetric outcomes, such as spontaneous abortion, preterm birth, small for gestational age (SGA), low birth weight (LBW) and congenital malformations (especially cleft lip and palate, urinary malformations, hypospadias and eye diseases) [17,18,58–62]. Our case could underline this association. The mother did not stop working before and during pregnancy and the foetus had not only the premature DA constriction but also congenital cataract, without any other risk factors. In addition, the first child was affected by lip and palate cleft.

### Table 1. Continued.

| Authors (Y) | Sample size N | Study design | MA (y) | Causative agent (Substance exposure/idopathic) | Dominant echo findings | GA at diagnosis (W) | Treatment | Delivery | GA at birth (w) | Postnatal presentation | Postnatal treatment and course |
|-------------|---------------|--------------|--------|-----------------------------------------------|------------------------|---------------------|-----------|----------|----------------|------------------------|-----------------------------|
| 170         | 32            | Idiopathic   |        |                                               | PSV, PDV and PI on DA, mild PR | 31                   | FU        | ND       | ND              | A                      | Uneventful                  |
| 171         | 36            | Idiopathic   |        |                                               | PSV, PDV and PI on DA, dilated RH, mild PR | 34                   | FU        | ND       | ND              | A                      | Uneventful                  |
| 172         | 25            | Idiopathic   |        |                                               | PSV, PDV and PI on DA, dilated/contractile RH | 32                   | FU        | ND       | ND              | A                      | Uneventful                  |
| 173         | 41            | Idiopathic   |        |                                               | PSV, PDV and PI on DA, mild TR, dilated RV, severe hydrops | 28                   | FU        | ND       | ND              | Neonate death           | Neonate death               |
| 174         | 17            | Idiopathic   |        |                                               | PSV, PDV and PI on DA | 38                   | FU        | ND       | ND              | A                      | Uneventful                  |
| 175         | 20            | Idiopathic   |        |                                               | PSV, PDV and PI on DA, mild TR | 32                   | FU        | ND       | ND              | A                      | Uneventful                  |
| 176         | 28            | Idiopathic   |        |                                               | PSV, PDV and PI on DA, dilated RH, hypertrophic RV, mild PR | 33                   | FU        | ND       | ND              | A                      | Uneventful                  |
| 177         | 39            | Idiopathic   |        |                                               | PSV, PDV and PI on DA | 33                   | FU        | ND       | ND              | A                      | Uneventful                  |

GA: gestational age; W: weeks; Y: years; D: days; M: months; H: hours; FU: follow up; N: case number; MA: maternal age; RV: right ventricle; RA: right atrium; RH: right heart; PA: pulmonary artery; PuV: pulmonary valve; LF: left ventricle; PI: pulsatility index; DV: ductus venosus; PSV: peak systolic velocity; PDV: peak diastolic velocity; TR: tricuspid regurgitation; PR: pulmonary regurgitation; PS: pulmonary stenosis; RVOTO: right ventricle outflow tract obstruction; ND: no data available; CS: caesarean section; VD: vaginal delivery; PH: pulmonary hypertension; A: asymptomatic; CPAP: continuous positive airway pressure; IPPV: intermittent positive pressure ventilation; NO: nitrous oxide; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; SVT: supraventricular tachycardia; GDM: gestational diabetes; CTG: cardiotocography; ALGS: Alagille syndrome; WS: Williams syndrome; PPS: peripheral pulmonary stenosis.

Figure 4. Distribution of etiopathogenesis of human cases in literature no NSAIDs or CHD induced.
cardiovascular defects [63]. Also aromatic amines and aldehydes could have a role in COX2 inhibition that determine congenital heart defects [64]. In humans, malformations and cytogenetic effects have been observed among the offspring of women exposed to glycol ethers during pregnancy [65]. Some studies [66–69], but not others [70], report an excess risk of spontaneous abortion among women occupationally exposed to solvents. A small prospective cohort [71], and a meta-analysis [72], performed by the same research group both report associations between maternal occupational exposure to solvents and major malformations. Two occupational cohort studies of women working in laboratories suggest similar results [73–74]. Various case-control studies have shown relations between maternal occupational exposure to solvents and some subtypes of malformations, mostly oral clefts [75–77]. Some significant associations have also been reported between maternal exposure to solvents and cardiac malformations [75,78], visual impairment [17] and neural tube defects [75,79].

Conclusion

Premature constriction of DA is a rare event and in most cases is secondary to maternal intake of NSAIDs or foods rich in polyphenols. For the first time, the present review reported all cases of DA constriction not related to NSAIDs intake or to CHD.

The gynaecologist must take into account that there are not only forms of DA constriction secondary to the intake of NSAIDs. We assume a relationship between premature DA constriction and a maternal occupational exposure to solvents. This association between a maternal occupational exposure to solvents and an increased risk of adverse obstetrics outcomes has been widely discussed in the literature. In our case report and in the previous newborns this hypothesis is reinforced by the presence of other associated foetal malformations. It is therefore important to carry out through an occupational history and inform the patient about the potential risks associated with the exposure to solvents and toxic chemicals. Further investigation is needed to confirm their role in the pathogenesis of DA constriction, as in experimental animal models, such as those already performed in pregnant rats and sheep with polyphenols. A randomized clinical trial is needed to analyse the role of solvents in inducing this condition would be desirable, respecting the ethical aspects of the research.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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