Case report

HYDROPS FETALIS AND CONGENITAL PULMONARY CAPILLARY HAEMANGIOMATOSIS IN A PREMATURE INFANT - A CASE REPORT AND LITERATURE REVIEW

Authors:
Anna Iacoi[1], Alexander Brobeil[2], Malena Götte[1], Christian Enzensberger[1], Vera Müller[1], Stefan Gattenlöhner[2], Roland Axt-Fliedner[1]

1. Division of Prenatal Medicine, Dept. Ob&Gyn, Justus-Liebig-University, Gießen 2. Division of Pathology, Justus-Liebig-University, Gießen

Prenat Cardio 2018 Jan; 8(1):71-75
DOI: 10.1515/pcard-2018-0011

Abstract

Pulmonary capillary haemangiomatosis (PCH) is a rare disorder of the lung, well described in adult literature. PCH is characterized by capillary proliferation, infiltrating the interstitium and alveolar walls. This leads to development of respiratory distress and to end-stage pulmonary hypertension. Mostly young adults are affected. The affection of newborn is described in less than ten cases in literature in the past forty years. PCH is a mostly deadly ending disease. We present a preterm born infant with antepartal diagnosed hydrops fetalis, who died 30 minutes after birth. Autopsy revealed PCH as lethal reason and not cardial disease as presumed before.

Key words: *newborn, children, pulmonary capillary haemangiomatosis, pulmonary hypertension, prenatal sonography, hydrops fetalis*

INTRODUCTION

PCH is a very rare disorder, first described by Wagenvoort et al. in 1978[1]. It is bilaterally arising uncontrolled proliferation of pulmonary microvessels invading pulmonary structures resulting in diffuse alveolar haemorrhage. Histologically it is a low malignant, not metastasizing vascular neoplasm (Fig. 1). Clinically the patient shows dyspnoea and symptoms of pulmonary hypertension[2]. End-stage disease is characterized by right heart failure and death of the patient, if heart-lung-transplantation is not performed. Since 1978 there are less than hundred cases described in literature. Most cases are sporadic, but familial occurrence has been documented. The highest incidence is among 20-40 years of age. About 30 cases report about PCH in children[3,11]. In newborn this is an absolute rarity, with less than 10 cases reported in the last 40 years (see Table 1).

Hydrops fetalis is a condition in the fetus characterized by an accumulation of fluids or edema in at least two fetal compartments, including predominantly pleura, pericardium, abdomen and the skin. Underlying etiologies include a variety of either immune or non-immune causes.

So far a link between prenatal hydrops fetalis and PCH in the literature has not been described. We describe a newborn with PCH presenting with hydrops fetalis and right heart failure during third trimester of gestation.

How to cite this article:
Iacoi A, Brobeil A, Götte M, Enzensberger C, Müller V, Gattenlöhner S, Axt-Fliedner R. Hydrops fetalis and congenital pulmonary capillary haemangiomatosis in a premature infant - a case report and literature review. Prenat Cardio 2018 Jan; 8(1):71-75

CASE REPORT

A 28 years old 2G/1P was referred to our hospital at 32+4 weeks of gestational age with suspected tricuspid hypoplasy and symptomatic polyhydramnios. Non-immune Hydrops fetalis (NIHF, edema of the skin and mild pleura effusions) and intrauterine growth restriction below the fifth centile were present. In addition holosystolic tricuspid regurgitation was present in colour and PW-Doppler (interrogation 2.6 m/s). Forward flow within the normal sized pulmonary trunk and pulmonary arteries was documented. Cardiothoracic ratio and –circumference ratio were increased (CTR 0.56, CTCR 0.62). Umbilical and cerebral Doppler were normal. An increased pulsatility with a decreased forward flow during atrial contraction was present in the Ductus venosus (DV). Shortening fraction (SF) of the right ventricle measured by M-Mode was at the lower range of normal values (0.21). Otherwise cardiac anatomy was normal. Pulmonary circulation as interrogated by Colour- and Spectral-Doppler showed reduced blood flow. Karyotype has been determined through amniocentesis by first line physician (46, XX).

Corresponding author: Prof. Roland Axt-Fliedner, e-mail: roland.axt-fliedner@gyn.med.uni-giessen.de

Submitted: 05-01-2019, accepted: 15-01-2019

After amniondrainage of 1400 ml and induction of lung maturation a control next day showed stable fetoplacental circulation, unchanged tricuspid regurgitation, antegrade blood flow within the pulmonary trunk and restricted right ventricular function. At 33+2 weeks of gestational age the fetus presented with increasing pleural effusions and decreasing right ventricular SF (0.06). Tricuspid regurgitation was 2.3 m/s (fig. 2) and forward flow within the pulmonary trunk was still documented. However, increased pulsatility in ductus venosus with a-wave reversal, as well as severe polyhydramnios was registered. Myocardial deformation analysis based on two-dimensional speckle tracking revealed a ventricular global longitudinal peak systolic strain value of -16.6% (fig. 3 A), which is comparable to our recently published values in healthy fetuses[4,5]. In contrast, a massively reduced global longitudinal peak systolic strain of -7.9% was assessed (fig. 3 B). In view of the findings, showing decreasing right ventricular pump function, suitable with increased pulsatility in ductus venosus, in consultation with the paediatric colleagues caesarean section was performed the same day.

A preterm female newborn, weight 1490 g (P10), Apgar 5-0-0, arterial pH 7.39, was presented to the attending neonatologist´s team. Spontanous breathing was weak, the infant was cyanotic and pale. Heart rate fell from initial 80/min to 60/min, reanimation was started. She required intubation and ventilation, but she remained hypoxaemic despite high airway pressures. Performed x-ray of the chest showed pleural effusions, draining them showed no improvement in ventilation. After 30 minutes, reanimation was stopped and the newborn demised. Inspection of the infant showed a big head with head rind edema. Autopsy of the hypoplastic lungs demonstrated pulmonary capillary haemangiomatosis. The examination of the heart showed a slight enlargement with a patent foramen ovale and malformation of tricuspid valve. No genetic cause could be identified.

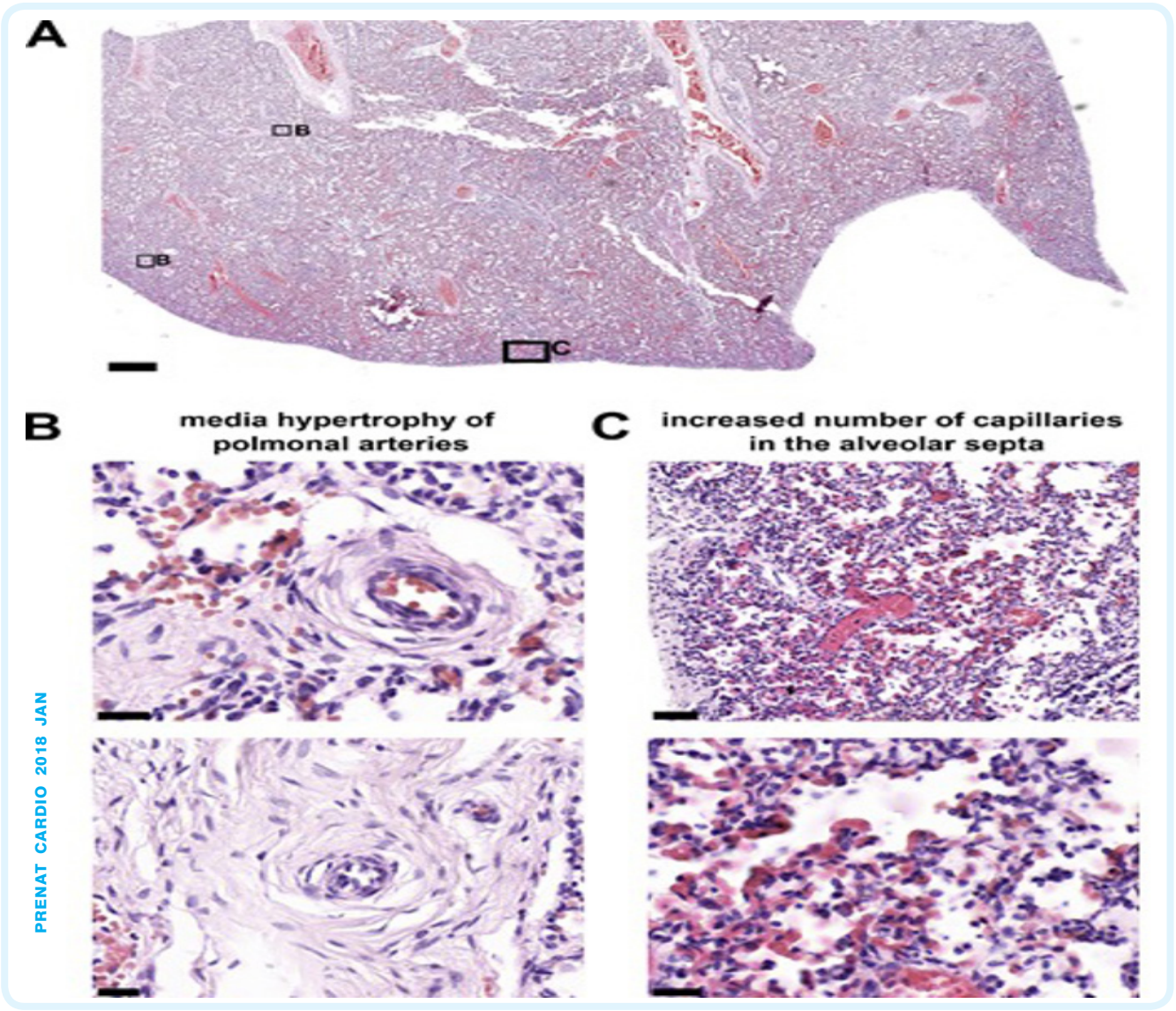

Fig. 1. A) Histological overview of the lung tissue with recognizable diffuse increase of the capillary blood vessels. Pulmonary arteries and pulmonary veins exhibit proper anatomical location. Bar: 200µm; B) Diseases related media hypertrophy of the pulmonary arteries with consecutive restriction of the vessel's lumen. Bar: 20µm; C) Alveolar septa show an in increase in erythrocyte filled capillary bulging out into the alveolar space. Bar: 20µm

DISCUSSION

PCH is not only a rare disease but also a mostly deadly ending one. Making a diagnosis is not easy, on the one hand because of its rarity on the other hand because of its similarity to other pulmonal disorders. PCH is distinguished from veno-occlusive pulmonal disease only through histological examination of lung tissue. However diagnostic parameters in adult patients and in children, clinically and radiologically[6], are already well described in literature. Nevertheless final diagnosis is made only through histological examination (open lung biopsy versus autopsy post mortem, Table 1, 2).

Diagnostic criteria in the newborn are not satisfactory known. Infact since 1978[1] there are fewer than 10 cases to be found in literature[3,6,7,8,9].

Various causes for non immune hydrops fetalis are described in literature. Despite rare metabolic diseases structural anomalies e.g. cardiovascular disorders have been described[10]. The presence of hydrops fetalis points out

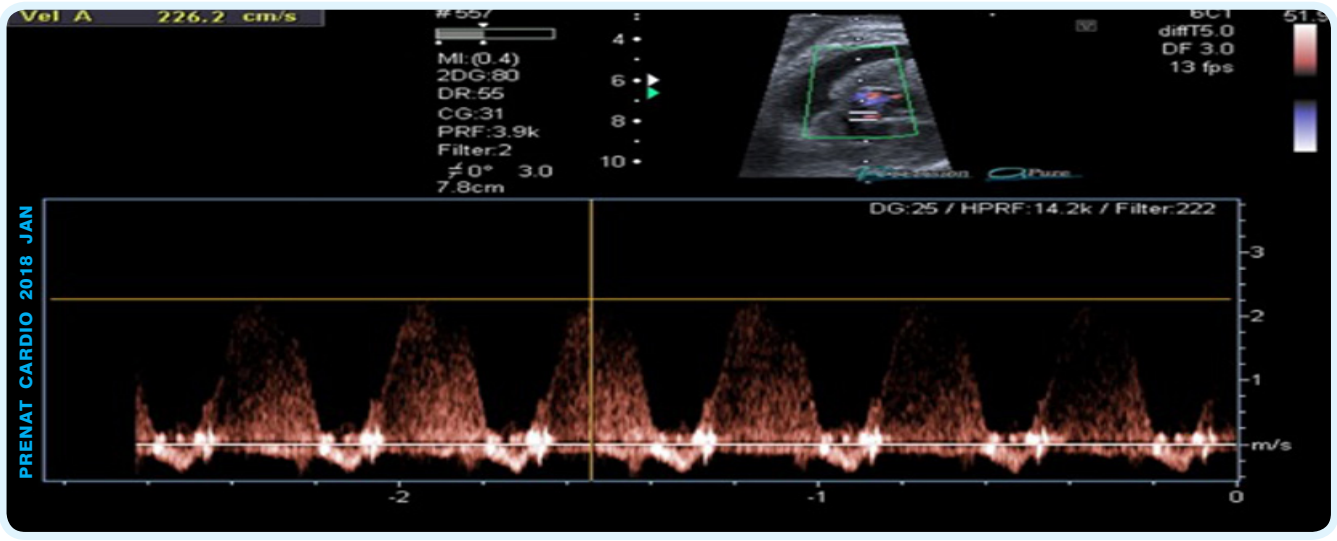

Fig.2: Tricuspid regurgitation of 226 cm/s in 330/7 weeks gestational age assessed by Puls-wave Doppler

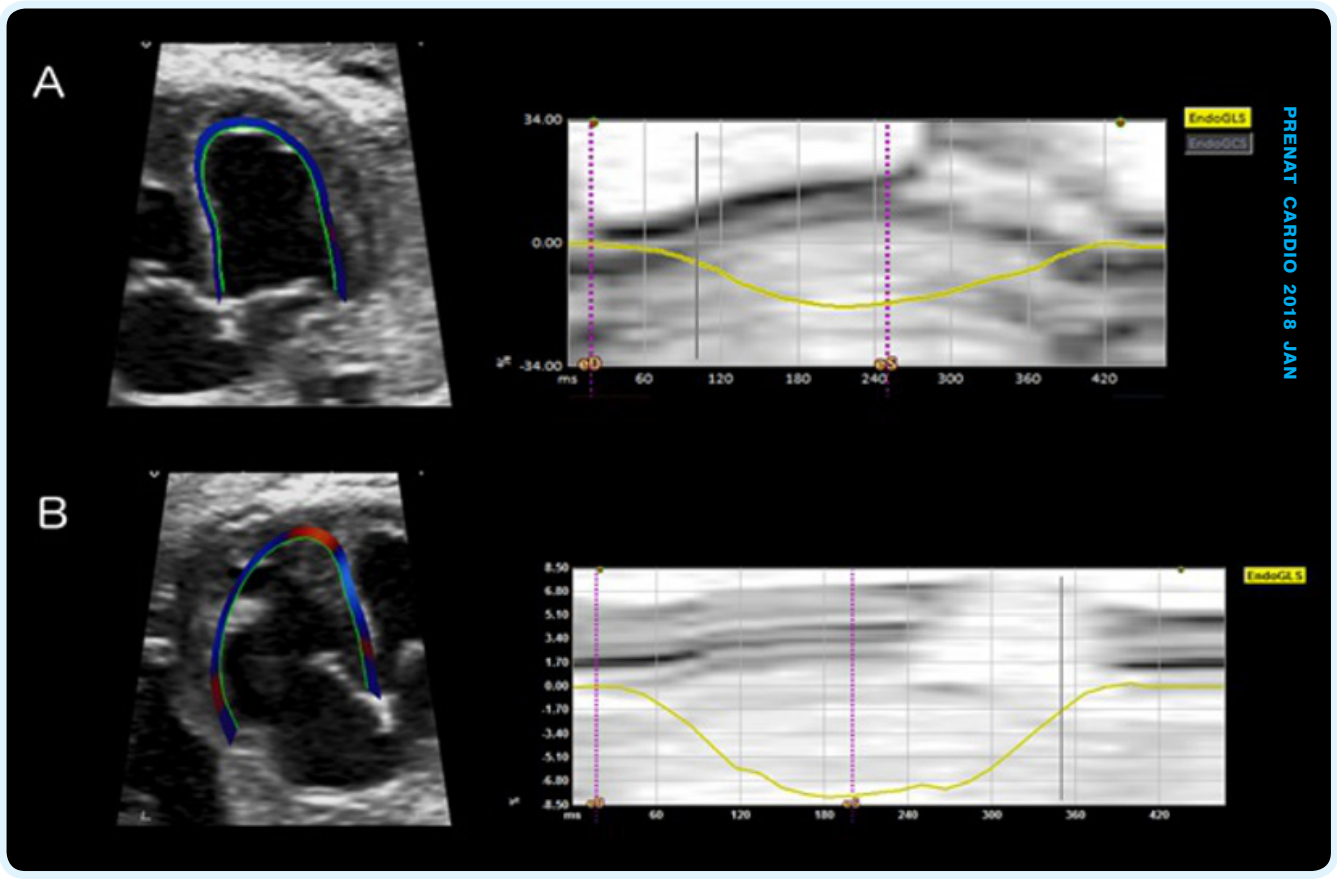

Fig. 3. Myocardial deformation analysis assessed by two-dimensional speckle tracking in 330/7 weeks gestational age: A (Left) Left ventricle with traced endocardium. (Right) Left ventricular global longitudinal strain (%) curve for one fetal cardiac cycle; B (Left) Right ventricle with traced endocardium. (Right) Right ventricular global longitudinal strain (%) curve for one fetal cardiac cycle.

severe disorder in the fetus. All the different disorders that are possibly causing hydrops fetalis are difficult to distinguish from each other prenatally. Outcome of these infants is highly depending on the cause of hydrops fetalis. This could be decisive in postnatal management. According to our case, PCH should be encountered as a rare cause of NIHF due to progressive right heart dysfunction in consequence of pulmonary hypertension, which could be demonstrated by massively reduced right ventricular global longitudinal peak systolic strain. Right heart failure then would translate into elevated right atrial pressures, increased intravascular pressure in the precardial venous and lymphatic system and thus leading to hydrops fetalis.

Sex	Prenatal findings	Age at presentation	Symptoms	Diagnostic	Age at death	Diagnosis
Female **34 GW** (Present case)	**Hydrops fetalis** **IUGR** **Tricuspid regurgitation** **ASD II** **Polyhydramnion**	**Directly after birth**	**Respiratory distress**	**Pleural effusions** **pneumothorax**	**30 minutes**	**Autopsy**
Male **30 GW** **Stillborn Twin** (Oviedo et al)	Oligohydramnion Fetal bradycardia			Hypertrophic cardiomyopathy Pleural effusions, Hydrops fetalis Renal and urinary bladder agenisis		Autopsy
Male **36 GW** (Sposito Cavallo et al		Directly after birth	Respiratory distress	x-ray, CT: bilateral opacities tricuspid regurgitation	8 months	Lung biopsy
Male **At term** (Dello Russo et al)		Directly after birth	No spontaneous breathing 21 h after birth: Respiratory distress pulmonal Hypertension	x-ray: Hypodiafania of right hemithorax Sonography: wet lung disease	3 days	Autopsy
Male **38 GW** (Oviedo et al)	IUGR Maternal anemia	12 days	Respiratory distress Mild pulmonary hypertension	x-ray: Cardiomegaly Tricuspid regurgitation Patent foramen ovale Patent ductus arteriosus	67 days	Autopsy
Male **31 GW** (Silva et al)	IUGR ASD II	18 days	Respiratory distress Mild pulmonal hypertension	ECHO: large ASD x-ray thorax: opacities CT: diffuse bilateral ground glass opacities Septal thickening	At least 27 months	
Male At term (Mc Govern et al)	Tracheo-Osophageal fistula (no genetic abnormalities found)	Directly after birth	Respiratory distress ASD II Moderate VDS Pulmonary hypertension	CT: ground glass opacities Bilateral pleural effusions Septal thickening EIF2AK4 neg.	3 months	Autopsy
Female 35 GW (Mc Govern et al)		6 weeks	Respiratory distress Pulmonary hypertension	X-ray thorax: alveolar opacity CT: ground glass opacities	12 months	Autopsy

Table 1: Reported cases of PCH in newborn

Pulmonary Hypertension	Pulmonary Capillary Hemangiomatosis
Interstitial fibrosis if hypoxia	Preserved architecture with areas of involvement mixed with areas of normal lung
Organizing thrombi	Intra-alveolar hemosiderin-laden macrophages, small areas of acute or old hemorrhage, hemosiderosis
Changes in major vessels	Proliferation around bronchovascular bundles creating nodular appearance. Bland endothelial cells, no mitoses.
Small vessels have medial hypertrophy and intimal fibrosis narrowing lumina to pinpoint	Proliferation of benign appearing capillaries expanding alveolar septa that appear to compress pulmonary veins At least 2 layers of aberrant capillaries within alveolar wall
Plexogenic arteriopathy, tuft of capillaries spanning lumina of arteries	Small pulmonary arteries with intimal thickening/ medial hypertrophy

Table 2. Pathology characteristics of Pulmonary Hypertension and Pulmonary Capillary Hemangiomatosis

There are eight well described cases in the literature (see Table 1). However prenatal examinations are mostly not described. IUGR was described in three infants[3,8]. There seems to be a complex of symptoms that connect the since yet described cases of PCH in newborn. If malformation of the heart is described, the presence of hydrops fetalis is conceivable, too. It seems, although numbers of cases are low, that a connection of hydrops fetalis, IUGR, tricuspid regurgitation and patent foramen ovale may be connected with the presence of PCH in the fetus.

All in common seems to be the presence of pulmonary hypertension. There is one case of a newborn without pulmonary hypertension[6]. Nevertheless the infant showed respiratory insufficiency and died of this with only 8 months, lung heart transplantation had not been possible.

Mc Govern et al.[9] presented two infants with PCH, who both had ground glass opacities in CT examination as well as septal thickening and small pleural effusions. This symptoms can be found in most of the other cases.

Postnatal treatment of this respiratory insufficiency with sildenafil, corticoid and interferon therapy as well as with angiogenetic inhibitors and even doxycycline has been described[8,11]. A young man with PCH and treated with doxycycline showed complete remission of symptoms[12]. So these treatments seem to prolong life of the patients. As we can see in the Table 1, there are infants who lived up to two years and even had episodes of life outside hospital.

There seems to be a genetic cause, two causative genes are identified, EIF2AK4 and FOXF1[14,15]. Nevertheless not all PCH cases show a mutation in these genes. The only curative treatment is heart-lung-transplantation, but there are conservative methods, that seem to prolong life of the patient and need further investigation. Radiology helps making diagnosis, x-ray and CT of the thorax show ground glass opacities, still final diagnosis can only be made through histological examination of lung tissue through open lung biopsy or in the end through autopsy of the whole lung.

There is a lack of prenatal diagnostic markers through sonography. The connection of hydrops fetalis and PCH is still unique. It seems likely that there are similarities to find even prenatal, since postnatal similarities are high. This should find attention in pre- and postnatal treatment of infants with hydrops fetalis with tricuspid malformation or patent foramen ovale and respiratory insufficiency after birth. Eventually other similarities can be found through prenatal sonography. It shows importance of prenatal sonography, especially in pregnancies with abnormalities of heart and lung in the fetus

References

1. *Wagenvoort CA, Beetstra A, Spijker J (1978) Capillary hemangiomatosis of the lungs. Histopathology 2: 401-406*

2. *Eltorky MA, Headley AS, Winer-Muram H, Garrett HE, Jr Griffin JP. Pulmonary capillary haemangiomatosis: a clinicopathologic review. Ann Thorac Surg 1994; 57:772-776*

3. *Oviedo A, Abramson LP, Worthington R, et al (2003) Congenital pulmonary capillary hemangiomatosis: report of two cases and review of the literature. Pediatr Pulmonol 36: 253-256*

4. *Enzensberger C, Achterberg F, Graupner O, Wolter A, Herrmann J, Axt-Fliedner R, Wall-motion tracking in fetal echocardiography-Influence of frame rate on longitudinal strain analysis assessed by two-dimensional speckle tracking. Echocardiography, 2017 Jun; 34(6):898-905*

5. *Enzensberger C, Achterberg F, Degenhardt J, Wolter A, Graupner O, Herrmann J, Axt-Fliedner R, Feasibility and Reproducibility of Two-Dimensional Wall Motion Tracking (WMT) in Fetal Echocardiography. Ultrasound Int Open. 2017 Feb; 3(1): E26-E33*

6. *Sposito Cavallo SL, Macias Sobrino LA et al (2017), Congenital pulmonary capillary hemangiomatosis in a newborn, Arch Agent Pediatr, 115 (1): e17-e20*

7. *Dello Russo P, Franzoni A, Baldan F et al (2015), A 16q deletion involving FOXF1 enhancer is associated to pulmonary capillary hemangiomatosis. BMC Medical Genetics 16:94*

8. *Silva CJTA, Massie J, Mandelstam SA (2005),Pulmonary capillary haemangiomatosis in a premature infant. Pediatr Radiol 35: 635-640*

9. *Mc Govern E, McNally P, O`Sullivan M et al (2016), Infantile pulmonary capillary haemangiomatosis: a lethal form of pulmonary hypertension. Cardiology in the Young 26: 663-668*

10. *Smrcek JM, Baschat AA, Germer U, Gloeckner-Hofmann K, Gembruch U, Ultrasound Obstet Gynecol. 2001 May; 17 (5): 403-9*

11. *Bartyik K, Bede O, Tiszlavicz L et al (2004), Pulmonary capillary haemangiomatosis in children and adolescents: report of a new case and review of the literature. Eur J Pediatr 163: 731-737*

12. *Ginns LC, Roberts DH, Mark EJ et al. (2003), Pulmonary capillary hemangiomatosis with atypical endotheliomatosis: successful antiangiogenetic therapy with doxycycline. Chest 124: 2017-2022*

13. *Almagro P, Julia J, Sanjaume M, et al (2002), Pulmonary capillary hemangiomatosis associated with primary pulmonary hypertension. Report of 2 new cases and review of 35 cases from the literature. Medicine (Baltimore) 81: 417-424*

14. *Best DH, Sumner KL, Austin ED et al, EIF2AK4 mutations in pulmonary capillary haemangiomatosis. Chest 2014, 145:231-236*

15. *Langleben D, Heneghan JM, Batten AP et al. Familial pulmonary capillary hemagiomatosis resulting in primary pulmonary hypertension. Ann Intern Med 1988; 109: 106-109*

All authors certify that there is no actual nor potential conflict of interest in relation to this article.