THE SIGNIFICANCE OF AUTOPSY TO LOOK FOR EXTRACARDIAC ANOMALIES, DESPITE CORRECT PRENATAL DIAGNOSIS OF HYPOPLASTIC LEFT HEART SYNDROME IN TWO SIBLINGS

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Abstract

Thanks to recent progress in foetal imaging, it is now possible to detect many anatomical defects at earlier gestational age.

To illustrate the importance of prenatal diagnosis and the impact of extracardiac congenital anomalies we presented the cases of sibling with prenatal diagnosis of hypoplastic left heart syndrome (HLHS) and post-mortem diagnosis of adrenal hypoplasia.

Prenatal diagnosis was made in one mother twice, in two subsequent pregnancies, respectively at 22 and 18 weeks gestational age. The mother-to-be was referred to specialist foetal echocardiography because of suspected image of the heart. After the diagnosis was made, future parents were thoroughly informed about prognosis and possible management and decided to continue pregnancy, and treat a newborn, despite the fact that the foetal defect was diagnosed subsequently. The two newborns underwent surgical treatment and no complications occurred during the surgery. The children died after Norwood operation among the symptoms of acute adrenal failure. In post-mortem examination of the younger, the severe adrenal hypoplasia was identified.

Prenatal diagnosis enables to make informed, conscious decisions at appropriate gestational age. Detection of congenital heart defect should incline an ultrasonographer towards searching for extracardiac lesions, which might significantly influence prognosis and surgical outcomes.

Key words: *hypoplastic left heart syndrome, prenatal diagnosis, adrenal hypoplasia*

INTRODUCTION

The development of prenatal imaging techniques over the past two decades has enabled tracing of natural history, investigation of prenatal pathophysiology and determination of factors influencing early and late prognosis in congenital heart defects. It has also spurred the development of the principles of optimal perinatal care, including early intervention strategies within the cardiovascular system (IMPACT - Immediate Postpartum Access to Cardiac Therapy, EXIT- Ex Utero Intrapartum Therapy) in the most severe anomalies[1]. Also, in selected cases, prenatal interventions have been introduced[2].

According to EUROCAT (a European network of population registers of congenital defects), the average incidence of congenital heart defects (CHD) in Europe in 2008-2012 was about 8 per 1,000 births, and the incidence of hypoplastic left heart syndrome (HLHS) was 2.74 per 10,000 births. In the same period, 22.6% of perinatal deaths were caused by CHD, a quarter of which constituted the cases of HLHS. The average pregnancy termination rate because of CHD without associated anomalies was 0.39 for 1000. In addition, 18% of CHD were accompanied by large extracardiac congenital malformations. Approximately half of the cases of pregnancy termination due to complex CHD were pregnancies complicated additionally by major extracardiac malformations. HLHS is one of the most frequently detected heart defects in prenatal echocardiography. The detection of HLHS in ultrasound screening performed by gynaecologists is also on the rise, since it is relatively easy to diagnose in the classical

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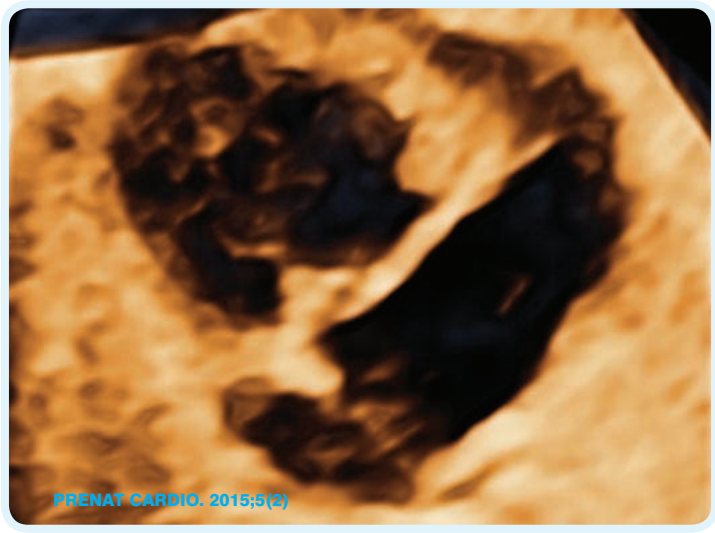

Fig. 1. Four-chamber view in systole in STIC technique. The image of abnormal heart.

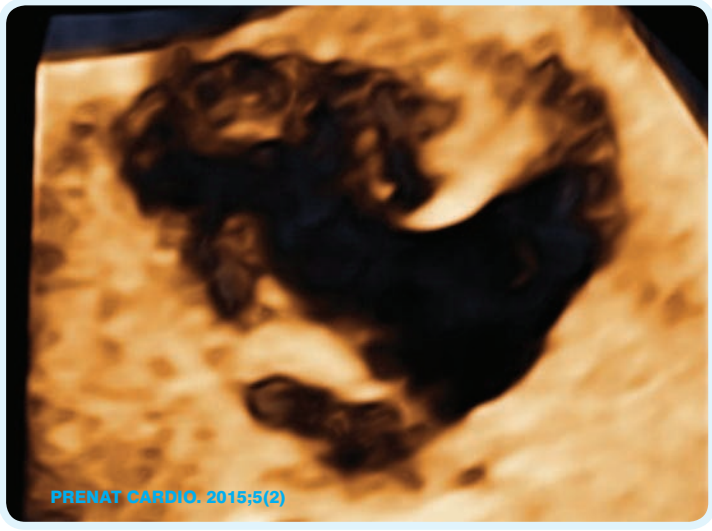

Fig. 2. Four-chamber view in diastole in STIC technique. The image of abnormal heart.

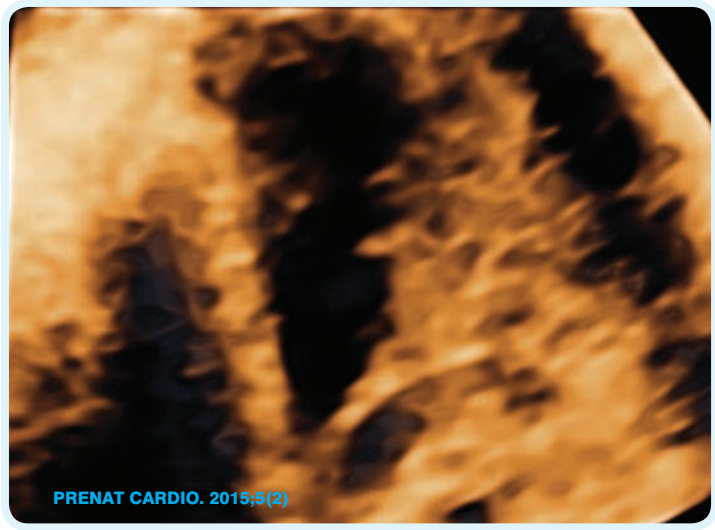

Fig.3 Three-vessel view in systole. Disproportion of the great vessels

four – chamber view. In approximately 20-28% of cases, HLHS is accompanied by extracardiac defects[3], of which 5-10% of cases are chromosomal anomalies and syndromes[4]. These anomalies significantly affect prognosis and prenatal counselling.

Congenital adrenal hypoplasia (CAH) is a very rare disease of X-linked or autosomal recessive inheritance. The incidence of X-linked congenital adrenal hypoplasia, which affects mainly males, is approximately 1 in 12,500 newborns. The onset and the clinical presentation of the disease can vary among affected individuals in the family and often leads to death.

This paper presents an extremely rare case of a pregnant woman whose two consecutive pregnancies were diagnosed with HLHS, and in the second one the autopsy of the newborn revealed accompanying severe adrenal hypoplasia. The family did not agree to post-mortem examination of the first newborn. The clinical course of HLHS associated with CAH in these cases turned out to be dramatic in comparison with the course of treatment of HLHS without associated extracardiac defects.

DESCRIPTION

In the presented cases, HLHS was diagnosed in the second trimester of pregnancy in one mother in two consecutive pregnancies at 22 and 18 weeks' gestation. Gravida was referred for foetal ultrasound examination due to suspected heart anomalies detected during the ultrasound screening performed each time by an obstetrician. During the examination, each time the features of classical form of HLHS were found: a small left ventricular cavity, dominant right ventricle, a narrow, hypoplastic ascending aorta [fig.1,2]. It revealed no inflow to left ventricle (LV) and outflow from LV in colour Doppler flow mapping. 3-vessel view (upper mediastinum) [fig.3,4] revealed widened pulmonary trunk and hypoplastic aortic arch back-filling from ductus arteriosus [fig.9]. An assessment of prognostic factors was made: there was no tricuspid regurgitation [fig.6,7], the spectrum of pulmonary venous flow in all foetuses was normal [fig.8], foramen ovale was non-restrictive (diameter 6 to 8 mm) [fig.5]. The stability of the foetal circulatory system was defined by Cardio Vascular Profile Score (CVPS), and in all cases 10 points were obtained. Flow spectrum in the middle cerebral artery in all foetuses did not show reduced impedance. None of the foetuses were diagnosed with extracardiac anomalies by prenatal ultrasound. Both underwent prenatal karyotyping, which yielded normal results.

The woman was subject to a particularly meticulous examination because her previous pregnancy was complicated by HLHS. No extracardiac anomalies were detected. Prenatal appointments were scheduled for follow-up visits every 3-4 weeks; during subsequent ultrasound examinations in both foetuses an average

degree tricuspid regurgitation was observed, which appeared to have decreased slightly in the last prenatal examination. As part of the prenatal assessment a space-time image reconstruction technique (STIC) was also used; images were stored in 3D, greyscale and mapped with colour Doppler (STIC images) [fig.9,10,11].

Following the diagnosis, parents were thoroughly informed about possible options. The possibilities of termination of pregnancy, continuation of pregnancy and planned, staged surgical treatment or comfort care after childbirth, were discussed in detail. The information was provided about each of the options in an exhaustive manner without focusing excessively on any of them. Finally, the parents decided to continue the pregnancy, and then decided to pursue palliative surgery. The course of the two pregnancies was uncomplicated. The pregnancies resolved through vaginal delivery and 1-minute Apgar score was 10 points for both newborns. Upon physical examination on the first day of life the condition of both newborns was good.

Prenatal diagnosis of HLHS was confirmed in both newborns through echocardiography performed immediately after birth. In all cases, wide PDA with bidirectional flow was visualized. Following the diagnosis, Prostin therapy was introduced and newborns were transported to the Department of Cardiology at University Children's Hospital (UCH) in Kraków.

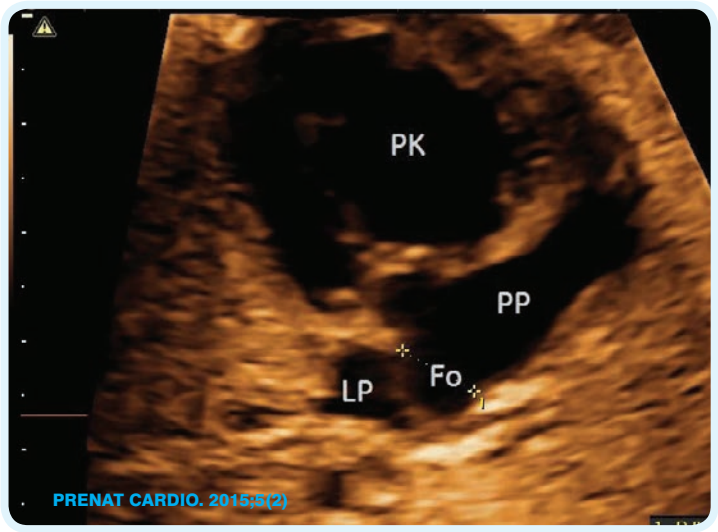

Fig.4. Non-restrictive foramen ovale

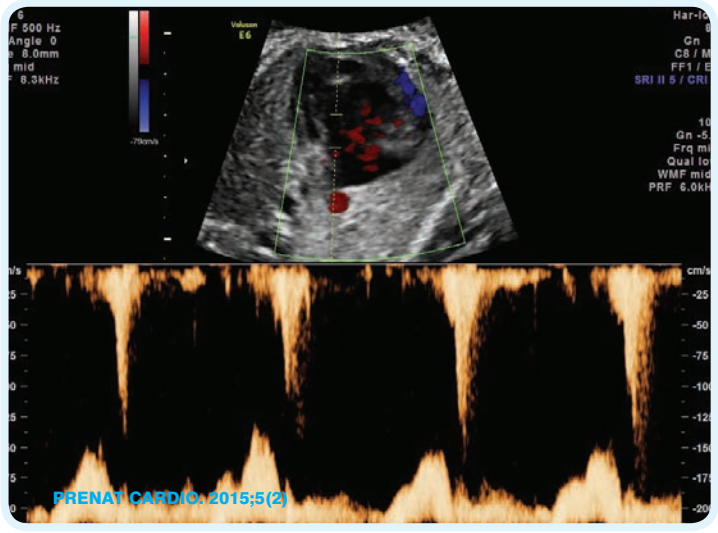

Fig.5. Protosystolic tricuspid regurgitation in pulsatile doppler

Both siblings were admitted in poor general condition. In one of them a few episodes of hypoglycaemia were reported and a tendency towards hyponatremia. The second one was admitted to the Neonatal Intensive Care Unit intubated, with assisted breathing, tachycardia, hyponatremia and symptoms of heart failure. All disorders were attended to as they occurred.

After cardiological consultation, the children were qualified for surgical treatment and were transferred to the Department of Cardiac Surgery at UCH in Kraków. The siblings qualified for urgent surgery due to unstable clinical status.

In both patients, modified Norwood procedure in extracorporeal circulation and general hypothermia was performed (at 5 - 8 days of life) as the first step of staged palliative surgery for HLHS.

In the postoperative period the siblings died, at 8 and 24 days after surgery respectively, due to shock and multiple organ failure resistant to conventional therapy. Post-mortem examination of the first one was not performed due to lack of family consent. The autopsy of the second sibling, performed upon consent of the family, revealed severe adrenal hypoplasia. Pathological examination demonstrated the presence of cells with large vacuoles resembling foetal adrenal cortex cells[5].

DISCUSSION

The treatment of hypoplastic left heart syndrome in a classic, isolated form, without chromosomal abnormalities or associated extracardiac anomalies, is carried out with increasingly satisfying early and late surgical outcomes in many centres all over the world[6-8]. Particularly problematic, however, are cases of extreme HLHS morphology (extreme hypoplasia of the ascending aorta with diameter less than 2 mm, tricuspid insufficiency, restriction or absence of interatrial communication, right ventricular dysfunction) and the cases of newborns affected by additional risk factors (low birth weight, chromosomal anomalies and syndromes of congenital malformations, extracardiac defects). These newborns are often admitted to departments of cardiac surgery in critical condition, with indications for immediate surgical intervention, which additionally increases the perioperative risk and steals the time required for diagnostic imaging and laboratory tests.

More widespread performance of prenatal ultrasound examination, with a detailed assessment of the heart, leads to an early diagnosis, which is beneficial in terms of enhanced preoperative care, resulting in lower overall mortality[9]. In one study, it was demonstrated

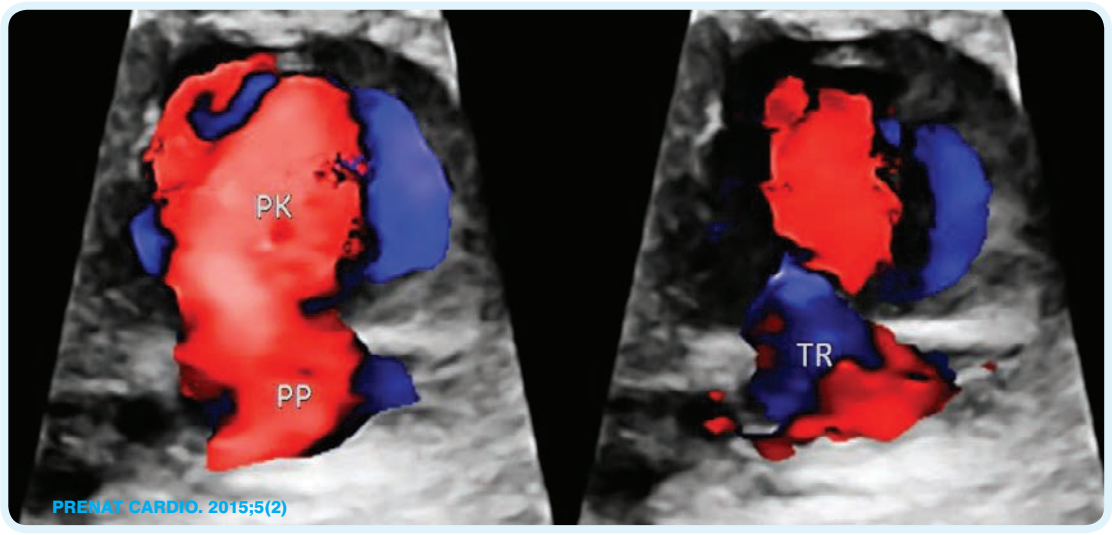

Fig.6. Colour doppler flow mapping of the heart of the foetus with HLHS. Tricuspid regurgitation. Diastole (left) and systole (right) in 4-chamber view.

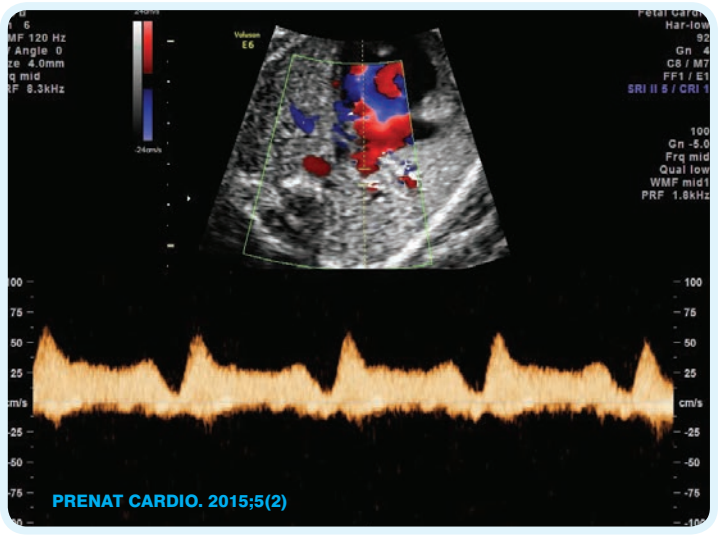

Fig.7. Normal spectrum of pulmonary venous flow in pulsatile doppler

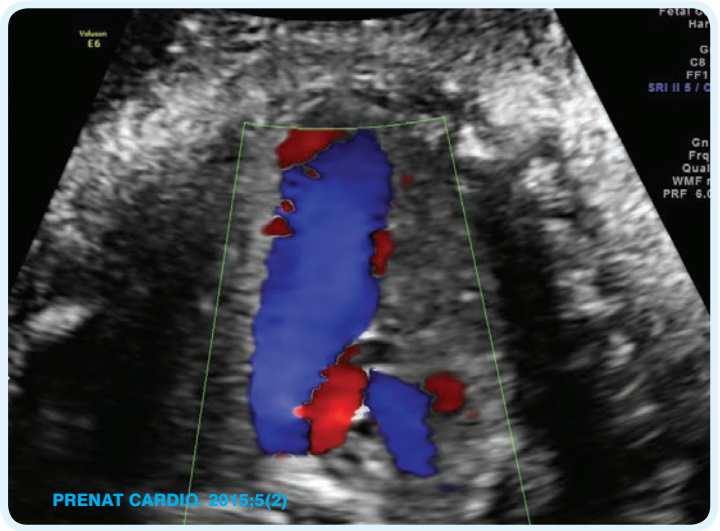

Fig.8. Reverse filling of aortic arch (red) through the ductus arteriosus in 3-vessel view

that the prenatal diagnosis of HLHS, despite being made in severe cases, was associated with a less frequent need of mechanical ventilation during the preoperative period, antibiotic therapy, cardiac catheterization and emergency surgery[10]. Comparing the results of surgical treatment of newborns diagnosed prenatally and those who were diagnosed after birth, it should be noted that children with HLHS who have not been diagnosed prenatally often die prior to being admitted to a cardiac centre and that children diagnosed postnatally represent a selected group who survived circulatory collapse and transportation[11].

In cases presented in this paper, it can be concluded that the early diagnosis of heart defects before birth fulfilled its premises. After birth, adequate medical care was undertaken, thus avoiding severe deterioration of clinical status. It should be pointed out that the situation that occurred to the mother of siblings, whose two subsequent pregnancies were diagnosed with a severe complex heart defect, was particularly dramatic. Although the adrenal pathology was not diagnosed upon prenatal ultrasound in any of the siblings, prenatal and early postnatal care was uncomplicated. The mother consciously took the risk to continue the second pregnancy to term, despite an earlier traumatic experience of child loss. Despite the normal karyotype of both of the newborns, there was a lack of information from the autopsy of the first child (to which the parents did not agree). If clinical signs of adrenal insufficiency had been confirmed by the autopsy of the first child, detailed diagnostics of adrenal glands during the prenatal period could have been performed. This information could have also had an impact on the decision regarding the early termination of the pregnancy (the heart defect was recognized at 18 weeks' gestation). In the early postnatal period both the first and the second of described siblings were admitted to UCH in Cracow with indications for emergency surgery due to cardiovascular instability. This prevented accurate diagnostics of adrenal insufficiency, although it might have been one of the causes of instability and poor clinical status.

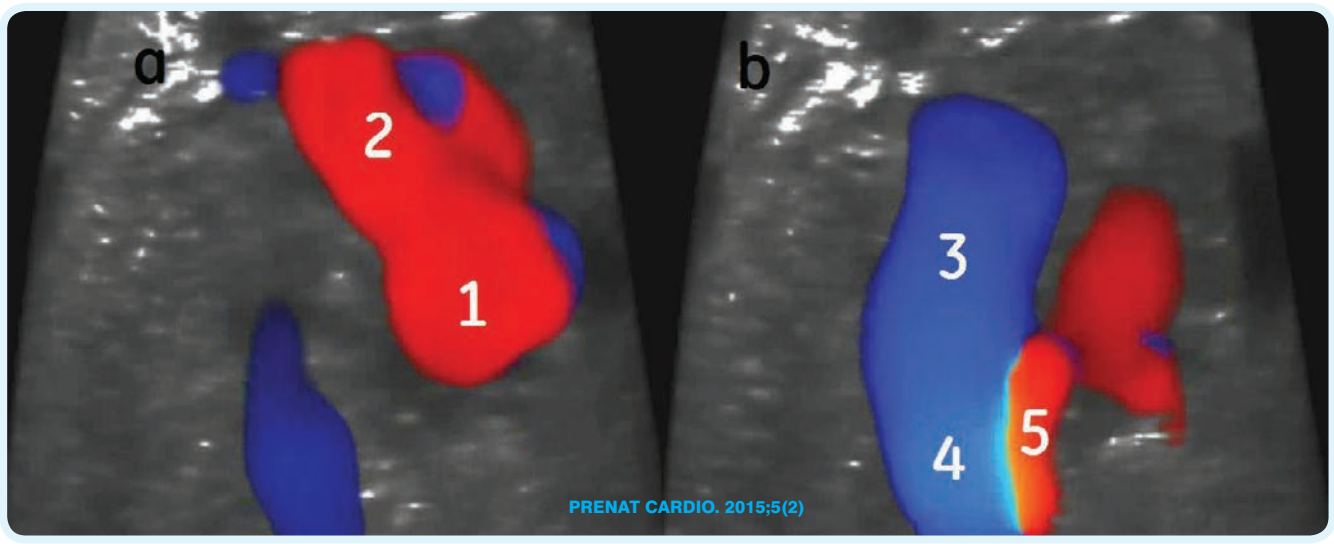

Fig.9. STIC color "glass body" 3D reconstruction: a) 1- right atrium, 2- right ventricle, b) 3- pulmonary trunk, 4-ductus arteriosus, 5-transverse section of aortic arch

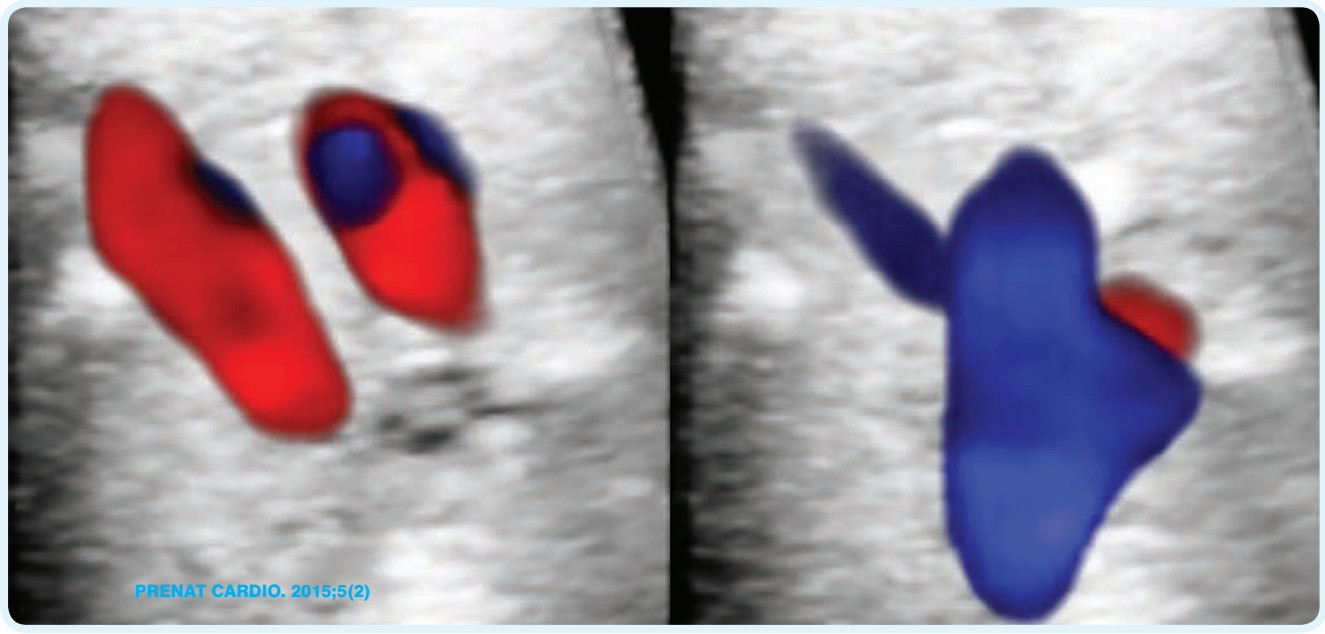

Fig.10. To compare, STIC color "glass body" reconstruction in normal fetal heart

Congenital adrenal hypoplasia is a rare anomaly whose prenatal detection and demonstration in prenatal screening imaging is difficult[12]. In reported cases in literature, even magnetic resonance imaging has not showed any abnormalities of the examined organs[13]. Prenatal diagnosis of congenital adrenal hypoplasia has not been described yet in literature. The association of congenital adrenal hypoplasia with HLHS did not facilitate the diagnosis and clinical symptoms of heart failure and respiratory distress overlapped with symptoms of adrenal insufficiency. The onset of this severe anomaly may be asymptomatic or scantily-symptomatic, followed by a sudden collapse of the clinical condition with the symptoms of life-threatening shock resistant to treatment[3]. In milder forms, the disease can manifest itself by hyponatremia, hypoglycaemia, lack of weight gain, nausea, vomiting, seizures, and respiratory disorders[5].

Familial occurrence of adrenal hypoplasia with severe symptoms appearing in neonatal period leading to death was also described. The post-mortem studies have shown significantly reduced adrenal glands of abnormal structure, large adrenal cells with greater, irregular nuclei and large vacuoles as well as the presence of fat and connective tissue[12,14].

The detection of adrenal hypoplasia in newborns by means of screening tests is unfortunately impossible because it is cumbersome to implement adrenal function tests in all newborns. The problem becomes even more complex if in a symptomatic newborn symptoms of the defect overlap with symptoms of acute cardiopulmonary failure that occur in children with hypoplastic left heart syndrome.

Prenatal diagnosis allows families to make informed, conscious decisions, at the appropriate stage of pregnancy[15]. Detection of the complex congenital heart disease should prompt a thorough investigation for extracardiac defects, which can significantly affect the prognosis and outcome of surgical treatment, especially in high-risk foetuses[16]. Despite the advances in prenatal diagnosis and adherence to existing procedures, these defects are difficult to diagnose in routine medical management. Our observations indicate also the importance of an autopsy examination in newborns despite prenatal and postnatal imaging techniques.

Conflict of interest: author declare no conflict of interest

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