Original **paper**

RETROSPECTIVE ANALYSIS OF PRENATAL ECHCARDIOGRAPHY FINDINGS IN CASES OF CONGENITAL HEART DEFECTS: COMPARISON WITH POSTNATAL PULMONARY HYPERTENSION REVEALED BY LUNGS HISTOPATHOLOGY (2010-2015)

Authors:
Hanna Romanowicz[1], Ewa Czichos[1], Katarzyna Zych-Krekora[2], Michał Krekora[3], Maciej Słodki[2], Maria Respondek-Liberska[2,4]

1. Department of Pathology Polish Mother's Memorial Hospital, Research Institute, 2. Department of Prenatal Cardiology, Polish Mother's Memorial Hospital, Research Institute, 3. Department of Obstetrics & Gynecology, Polish Mother's Memorial Hospital, Research Institute 4. Department for Fetal Malformations, Medical University of Lodz

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Abstract

Introduction:

It was retrospective analysis of prenatal echocardiography findings in fetuses with congenital heart defects, who died in our institution and had an autopsy exams in years 2010 - 2015.

Material and methods:

Among total 115 deaths the pulmonary hypertension based on histopathology criteria was present in 83 cases (72%) as a leading cause of their deaths. Out of 83 neonates 40 underwent prenatal echo, 43 did not, however in both groups there were similar types of heart defects.

Results:

The prenatal echo findings from study group (n=40), from the last echo before the delivery were compared with control group and group of HLHS who did survive neonatal surgery and were discharged from hospital. There were statistical differences between pulmonary artery/aorta ratio in fetuses in control group and fetuses in study group („pulmonary hypertension" after birth) (p=0,044). There were statistical differences between pre-delivery pulmonary artery/aorta ratio in fetuses in study group (with „pulmonary hypertension" after birth) and in group of fetuses with HLHS, alive & well after first surgery (p=0,027). There were no differences between pulmonary artery/aorta ratio fetuses in control group and fetuses with HLHS, alive & well after first surgery (p=0,38)

Conclusion:

1) Pulmonary hypertension was a frequent cause of neonatal deaths among our series of congenital heart defects

2) Dilatation of pulmonary artery (and increased pulmonary/artery ratio) in fetal echo just before delivery may be an important risk factor for poor neonatal outcome in congenital heart defects.)

Key words: *fetal echo, pulmonary artery, pulmonary hypertension after delivery, autopsy*

The prenatal diagnosis of congenital heart defects has been well established. However, even with an antenatal diagnosis, some neonates, despite planned delivery in the tertiary center and proper perinatal management, would not survive due to many reasons, among them, pulmonary hypertension.

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It is well known that prenatal restrictive foramen ovale, and or ductus arteriosus constriction or reversal flow in pulmonary veins may jeopardise the postnatal outcome. The goal of our research was to observe if there are any other prenatal echocardiographic features that may increase the risk of neonatal pulmonary hypertension and adverse outcome in fetuses with congenital heart defects.

Corresponding author: hanna-romanowicz@wp.pl

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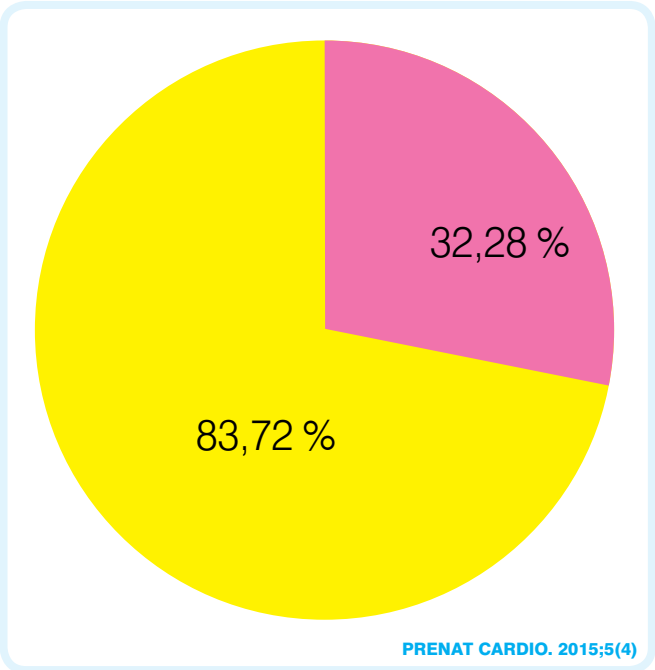

Fig. 1. Total number of autopsies in our Institute in years 2010 – 2015 (n= 115), divided into 2 groups: neonates with pulmonary hypertension n=83 (72%) and neonates without pulmonary hypertension n=32 (28%)

It was a retrospective evaluation of the medical records from the computer database and second evaluation of frozen frames and cine loop movies from the last echo exam before delivery to answer the question: is it possible to suggest neonatal "late" pulmonary hypertension? Moreover, based on what prenatal echocardiographic findings?

MATERIALS AND METHODS

We retrospectively identified all neonates with CHD who died in our Institute and underwent autopsy examination in years 2010 – 2015, and identified those who had pulmonary hypertension based on histopathological exams in Department of Pathology.

The exclusion criteria was: termination of pregnancy and intrauterine death.

The histopathology criteria of pulmonary venous hypertension[1,2,3,4,5], were such as presented in Table 1.

The total number of autopsies was 115 and in 83 cases (72%) pulmonary hypertension was noted (Fig.1); min 10, max 21 deaths per year (Fig 2).

The second part of the analysis was dedicated to the subgroup that had echocardiographic examinations in the Department of Prenatal Cardiology in our Hospital before delivery (Fig. 3). Out of 83 patients, 43 did not have prenatal echocardiography, and 40 underwent fetal echocardiography in our center.

Fetal echocardiograms were performed transabdominally using Voluson E8, Voluson 730 (GE Healthcare Ultrasound) or Philips Medical HDI. All examinations had digital storage.

All prenatal echocardiograms were reviewed from earlier recordings in order to double check the fetal heart size, FO size (the diameter of FO was measured between the superior and inferior limbs of the FO, where the FO flap was at its maximum leftward excursion during the cardiac cycle, from a four-chamber orientation of the fetal heart, with the plane of imaging perpendicular to the plane of the atrial septum), the diameter of pulmonary artery (PA), and aortic artery (Ao) in mediastinum where they were both visible at the same time, the diameter of PV branches, and, if available, the pattern and velocity of flow across the FO, and the pattern flow of the pulmonary veins at the left atrial junction. Tracings were obtained with the sample volume as parallel to the direction of blood flow as possible.

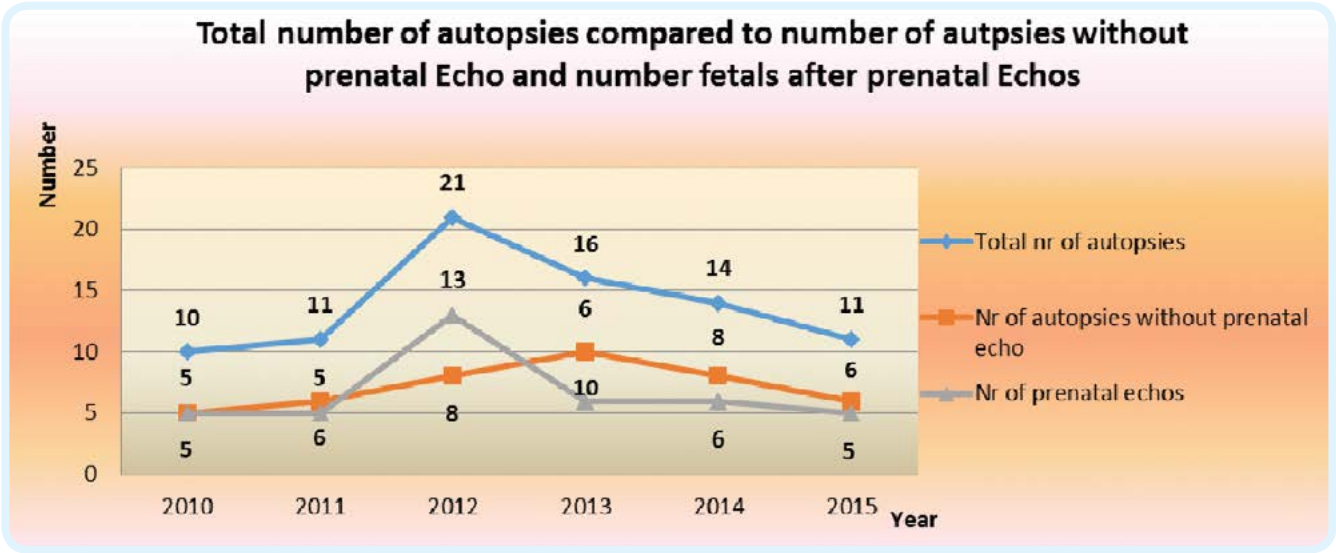

Fig. 2 Number of autopsy examinations of newborns with pulmonary hypertension (total n=83) in 2010-2015 and with no prenatal echo and after prenatal echo

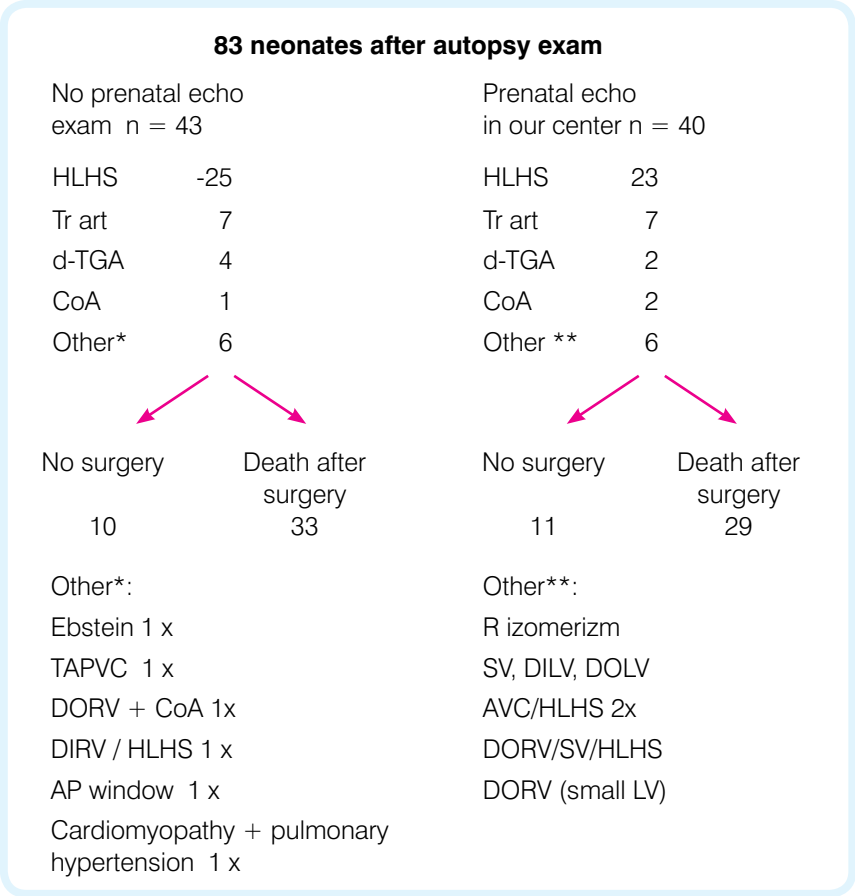

Fig. 3. 83 neonates with CHD and autopsy revealed pulmonary hypertension, divided into two groups : no prenatal echo n=43 and after prenatal echo n=40

The measurements of the pulmonary artery (in mm) and right pulmonary artery from the prenatal group were superimposed on normograms from Ruano [6].

Next step, the measurements of the pulmonary artery and aortic artery and pulmonary/aortic ratio, were compared in study group and our own normal control group (n= 134 fetuses) and in the group of fetuses with HLHS (n= 14), who after surgery were in good condition and were discharged from the hospital.

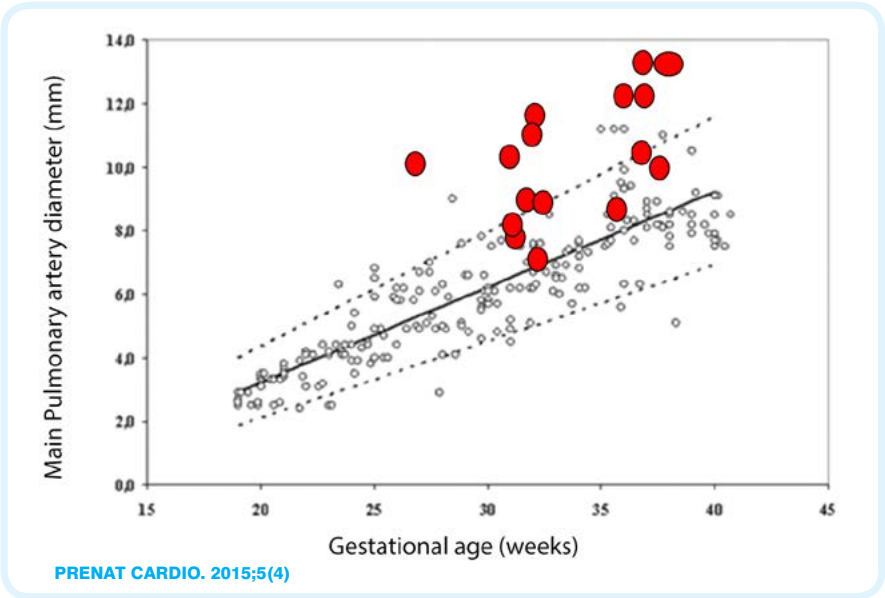

Fig. 4. Measurements of pulmonary artery diameter from the prenatal study group superimposed on the Ruano normogram. (n= 16 fetuses)

For statistical analysis Shapiro-Wilk test was used to check if there was normal distribution and t-Student test to compare the 3 groups. Cut off value of 0,05 was accepted.

The fetal PV flow pattern was considered normal in the event of forward flow in ventricular systole and diastole, questionable with cessation of flow or small a-wave reversal during atrial systole and abnormal in the case of reversal of the a-wave.

The time gap between last echo and time of delivery, fetal karyotype, type of delivery, birth weight, Apgar score and clinical outcome, were also evaluated.

RESULTS

Fetal echocardiography was performed min once, max 7 times per fetus (mean 2,5), with total 94 examinations in 40 cases in our referral center. The fetal echo measurements were analyzed from the last fetal echo before delivery.

In the prenatal group there were 25 cases of low-risk pregnancies and 15 cases of high risk pregnancies: 3x twins after IVF, 1 x twin spontaneous gestation after demise of the co-twin in 1st trimester, maternal infection in 1 trimester (4x), previous miscarriages (4x), maternal epi (1), maternal cholestasis (1) and 1 prenatal valvuloplasty of aortic valve at the 28th week of gestation.

In the prenatal group, in 35 fetuses NT were measured in 1st trimester and were 1,9 +/0,9 mm. Abnormal NT was present in two fetuses: 4,5 and 5 mm (first one with 45,XO the other one with SLO Syndrome: 46 XY and truncus arteriosus, female genitalia, syndactyly, microcephaly). In the other nine fetuses that underwent amniocentesis, normal karyotype and no genetic syndromes were suspected.

Fetal heart defects in prenatal subgroup were diagnosed at mean 23 +/-4 wks of gestation, and the last echocardiography exam was performed at mean 34,9 +/- 3 wks (Table 2). Appropriate gestational age was present in 31 fetuses and small gestational age (the difference between gestational age based on maternal last menstrual

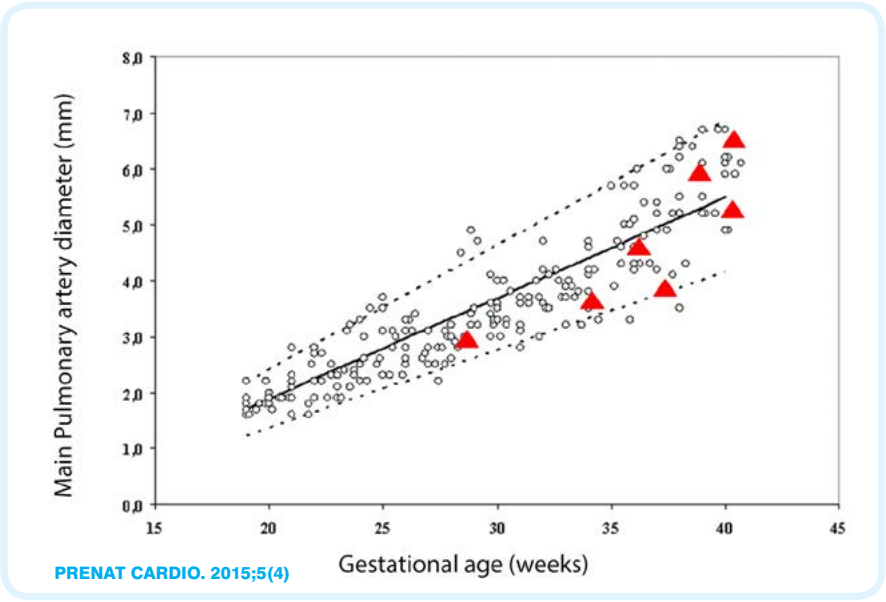

Fig. 5. Measurements of fetal right pulmonary artery diameter from the prenatal study group superimposed on the Ruano normogram (n= 7 fetues).

period and fetal biometry > 2 weeks) in 9 fetuses; mean umbilical PI was 1,1. There were 23 fetuses with HLHS, 7x Truncus arteriosus, 2 x d-TGA, 2 x CoA, 2 x Single ventricle, 1 x AVC, 1 x Aortic stenosis evolving to HLHS, 1 x right isomerism and 1 x DORV with small LV.

In the prenatal group, extracardiac malformations and anomalies were present in 14 fetuses such as single umbilical artery 1 x, pyelectasis 1 x, esophageal atresia 1 x, situs inversus 1x, maternal myoma (8 cm) 1x, hydrops testis 1 x and in 6 fetuses placental thickness > 6 cm.

All fetuses based on the last echocardiographic exam were without congestive heart failure (CVPS 9,2+/0,7).

Delivery in the prenatal subgroup took place at mean 38,1 +/-1,4 wks, all in

Criteria of Hypertensive pulmonary vascular disease[1,2,3,4,5]
1. Distal extension of muscle into distal arterioles and medical thickening of muscular arteries.
2. Cellular intimal proliferation limited to small muscular arteries, usually mostly cellular endothelial reaction.
3. Medial hypertrophy and concentric laminar intimal fibrosis.
4. Progressive generalized arterial dilatation with plexiform lesions.
5. Chronic dilatation with medial as well as intimal fibrosis; prominent plexiform lesions, veinlike branches and angiomatoid lesions; pulmonary hemosiderosis
6. Necrotizing arteritis
as well as characteristic morphological indexes for congestive vasculopathy:
1. Pulmonary Arteries
-prominent medial hypertrophy and muscularisation of arterioles
- prominent eccentric, nonlaminar, nonobstructive intimal fibrosis over long distances
2. Pulmonary Veins
-medial hypertrophy and arterialization
- moderate intimal fibrosis
3. Lymphatics
-dilatation
4. Lung Tissue
-interstitial edema, interstitial fibrosis, hemosiderosis

Table 1:Criteria of Hypertensive pulmonary vascular disease[1,2,3,4,5]

Maternal age mean and STD	29,21053 4,674443
High-risk pregnancies- number of cases	15
Low-risk pregnancies- number of cases	24
First pregnancies – number of cases	22
Subsequent pregnancies – number of cases	17
Mean NT in the first trimester in 35 fetuses	1,9 +/0,9
Mean gestation age of fetal heart defect detection	23 +/4 wks
Mean gestational age of the last fetal echo	34,9 +/-3 wks
Small gestational age - number of cases	9 fetuses
Males – number of cases	21
Females – number of cases	17
Prenatal sex undetermined	2
CVPS	9,2 +/0,7
Cesarean sections / Vaginal deliveries (number of cases)	33/ 7
Gestational age upon delivery in weeks	38,1 +/-1,4
Neonatal birth weight (g)	2955+/-469
Apgar score	8+/-1,5
Mean time of neonatal cardiac surgery (days)	15 +/8
Death (100%)	27+/-17 days
No surgery	11 neonates
Death after surgery	29 neonates/ infants
Mean PA/AO ratio	3,3

Table 2 : Clinical data of prenatal subgroup n=40

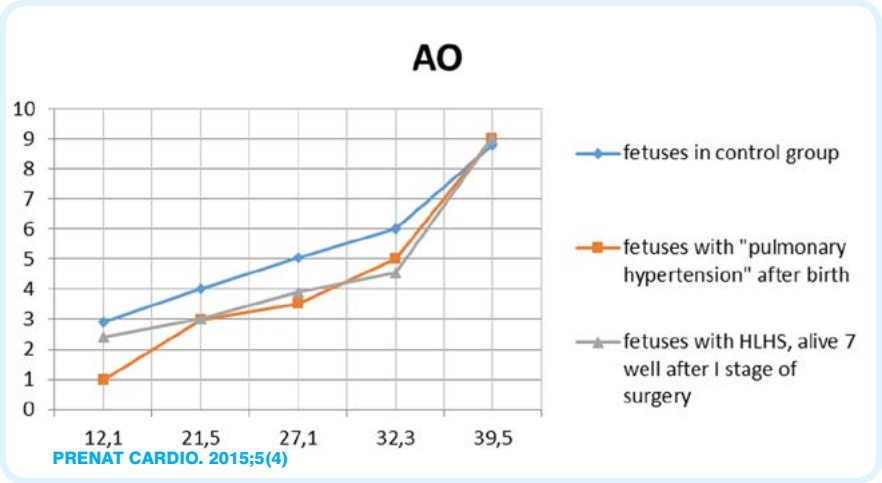

Fig. 6 Ao measurements in upper mediastinum versus gestational age in control group, fetuses with congenital heart defects who died after birth and had pulmonary hypertension in histopathology exam and in a group of fetuses with HLHS, who were alive & well after neonatal surgery

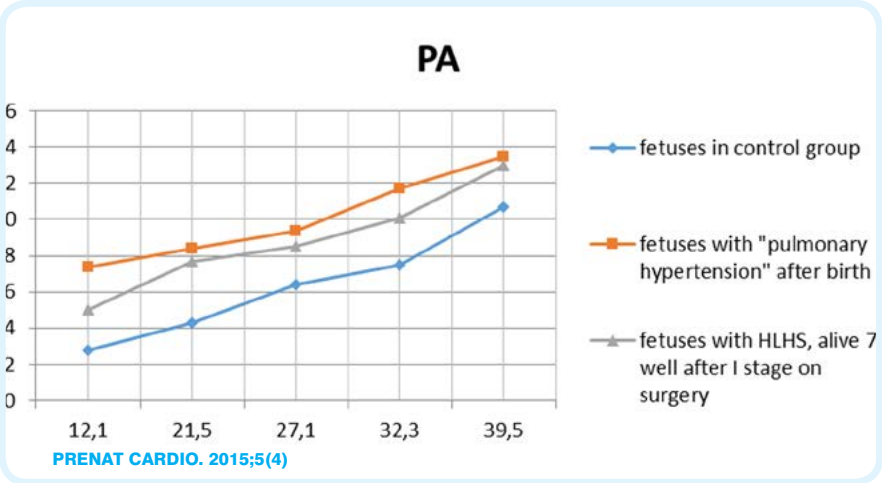

Fig. 7 PA measurements in upper mediastinum versus gestational age in control group, fetuses with congenital heart defects who died after birth and had pulmonary hypertension in histopathology exam and in a group of fetuses with HLHS, who were alive & well after neonatal surgery

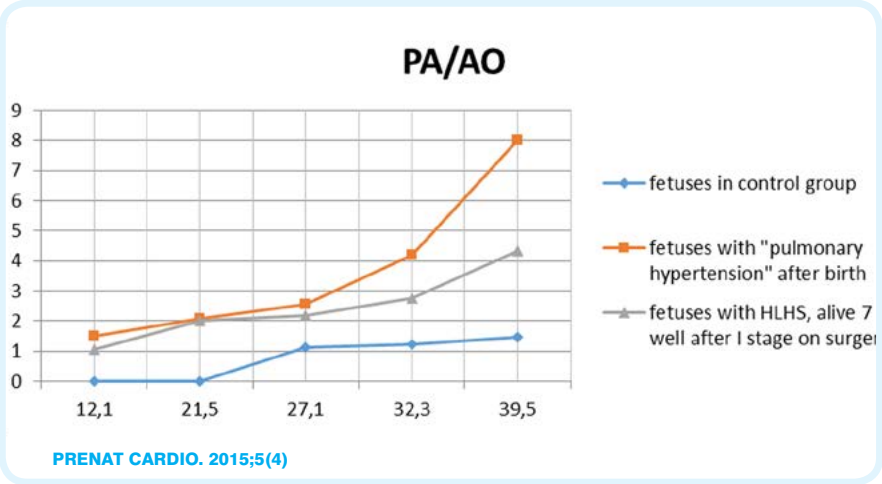

Fig. 8 PA/ Ao ratio versus gestational age in control group, fetuses with congenital heart defects who died after birth and had pulmonary hypertension in histopathology exam and in a group of fetuses with HLHS, who were alive & well after neonatal surgery

our institution. There were 33 cesarean sections and 7 vaginal deliveries. There were 22 males, 16 females and in two cases the prenatal sex was visible but difficult to diagnose.

The mean birth weight was 2955+/-469g and mean Apgar score 8+/-1,5.

All but one neonate did not require respiratory support in the first day after delivery (in one case CPAP was introduced). All neonates from the prenatal group were delivered in our tertiary center, with known prenatal diagnosis, which was confirmed by neonatal echo, they received prostin in ductal dependent circulations, all were in good clinical condition before and after delivery. All of them died before discharge from the hospital and in all of them upon autopsy in addition to the confirmation of prenatal diagnosis pulmonary hypertension was established based on histopathology evaluation of the lung tissue (HR and ECz).

Mean time of neonatal cardiac surgery in the prenatal group was 15 days +/8 days, and the mean time of death was 27 days +/ 17 days (Table 2).

In five of the presented cases pulmonary hypertension was suspected based on clinical evaluation ("pulmonary hypertension" mentioned in final clinical diagnosis in medical records before autopsy).

There were statistical differences between PA/Ao ratio at 39 weeks of gestation in fetuses in the control group and fetuses in study group („pulmonary hypertension" after birth) (p=0,044)

There were statistical differences between PA/AO ratio at 39 weeks of gestation in fetuses in study group (with „pulmonary hypertension" after birth) and fetuses with HLHS, alive & well after first surgery (p=0,027)

There were no differences between PA/AO ratio at 39 weeks of gestation in fetuses in control group and fetuses with HLHS, alive & well after first surgery (p=0,38)

DISCUSSION

With the progress in prenatal cardiology, more fetuses undergo transfer in utero to tertiary centers, and there is more evidence that prenatal diagnosis may improve perinatal outcome in some congenital heart defects such as HLHS and TGA[7,8,9,10,11,12,13,14]. In tertiary center not only prenatal diagnosis is usually confirmed but based on foramen ovale echo assessment and pulmonary vein flow in 3rd trimester or just before delivery the subgroup of critical heart defects may be subtracted for further speed of perinatal cardiological "make up", especially in cases of restriction of the foramen ovale or prenatal constriction of ductus arteriosus, as known risk factors[8].

However still despite proper prenatal care, selected time and place of delivery, proper postnatal management and neonatal cardiac surgery some neonates die (even without foramen ovale restriction and/ or ductus arteriosus prenatal constriction) despite all of the efforts current medicine may offer them.

One of the causes of poor outcome is pulmonary hypertension, which is not always clinically evident and, therefore, difficult for early management, assuming as suggested by Wagenvoort [15] that it could be reversible at least at some stage of the disease.

Our data has shown that at our institution pulmonary hypertension was a leading cause of neonatal death, (10-20 deaths per year) despite prenatal *in utero* transfer, proper perinatal care, cardiology service and cardiac surgery within the same institution (Fig,1, 2).

So far, neonatal pulmonary hypertension was discussed mainly in prenatally detected TGA[9], HLHS[16] and congenital obstruction of pulmonary venous return[17] . However, our results and data from pediatric cardiology has shown that this anomaly may be present also quite often in other heart malformations such as truncus arteriosus as well as in other congenital heart defects.

As fetal circulation changes in 2nd and 3rd-trimester restriction of the foramen ovale is usually picked up very late in gestation[18,19]. It was interesting to see in our results of pulmonary artery and RPA measurements superimposed on normograms from Ruano, that it was obvious to see pulmonary artery dilatation in a majority of cases without evidence of RPA dilatation. However these last measurements were less frequently available for analysis.

None of our neonates with prenatally detected and diagnosed CHD had cyanosis or heart failure, all of them received prostin infusion, only one of them required CPAP for the first 4 hours of life, which indicate that clinical deterioration was silent in the first hours and days after delivery.

Early prenatal suspicion of pulmonary hypertension in the case of congenital heart defect may allow to consider neonatal inhaled nitric oxide therapy[20,21]. Alternatively, more precise genetic makeup in the future[22,23], or maybe better chosen time of cardiac surgery.

Limitations of this study: the lack of evaluation of characteristics of blood flow in the peripheral area of the lungs with color or power Doppler; lack of measurements of RPA and LPA in all cases, no application of the results in a subgroup of fetuses with truncus arteriosus

The strength of this study was: the highly selected data collected and prospectively analyzed fetal echocardiogram with complete follow-up from gestational age to postnatal follow-up and autopsy confirmation (without cases of termination of pregnancies).

CONCLUSIONS:

Pulmonary hypertension was a frequent cause of neonatal death among our series of congenital heart defects

Dilatation of pulmonary artery in fetal echo just before delivery may be an important risk factor for poor neonatal outcome in case of congenital heart defect.

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Divison of work:

Hanna Romanowicz: work with manuscript, references and final version

Ewa Czichos: providing the autopsy data and histopathology data and work with references:

Katarzyna Zych-Krekora: work with manuscript and references, submitting manuscript

Michał Krekora: work with manuscript, English correction,

Iwona Strzelecka: search of fetal data base, analysis for normal group

Paulina Kordjalik: search of fetal data base, analysis of the data, preparing charts,

Maciej Słodki: work with the manuscript, analysis of the data, references, final version

Maria Respondek-Liberska: concept of the research, manuscript editing, final version

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