Original **paper**

EARLY NEONATAL SURGERY FOR CONGENITAL HEART DEFECTS AFTER PRENATAL DIAGNOSIS OF RESTRICTED FORAMEN OVALE AS THE PRIORITY PROCEDURE?

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Abstract

From 2012-2014 we selected fetuses who had an isolated congenital heart defect and restriction of the foramen ovale defined as its diameter of 4 mm or less, shunt across foramen ovale, V max > 70 cm/sec along with a typical harsh sound during fetal ausculation during echocardiography and reversal flow in pulmonary veins, no extracardiac anomalies, singleton pregnancies and delivery > 37 weeks of gestation. It was retrospective analysis of 16 cases: There were 10 non-survivors and 6 survivors The only significant difference between survivors and non-survivors pertained to the fraction of newborns operated on up to 11th day, which was significantly higher among the survivors (5/6 vs. 2/8, p=0.031).

Conclusions:

1) In the event of prenatal restriction of the foramen ovale early surgery by day 10 had a statistically better outcome in terms of survival compared to cases that underwent surgery at a later period at our Institute.

2) Prenatal restriction of the foramen ovale was more often related to male gender and in 75% of cases in our series had complicated follow-up: neonatal death or prolonged hospital stay.3) Information from prenatal echocardiography regarding restriction of the foramen ovale should be taken into consideration as valuable information suggesting priority for early cardiac surgery

Key words: *prenatal restriction of the foramen ovale, early surgery, perinatal care*

INTRODUCTION

Neonate with an isolated ductal dependent congenital heart defect is usually a candidate for cardiac surgery, regardless of the prenatal diagnosis. However, in some cases, fetal echocardiography results provide important information and the priority of these selected cases, should be known to pediatric cardiac surgeons, before the neonate's clinical deterioration.

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MATERIAL AND METHODS

Based on our computer database in the years 2012-2014 we performed 3846 fetal echocardiography and ultrasonography examinations in 2366 pregnant women. From this material we selected fetuses who had an isolated congenital heart defect and restriction of the foramen ovale defined as its diameter of 4 mm or less, with across foramen ovale, V max > 70 cm/sec blood flow across foramen ovale along with a typical harsh sound during fetal ausculation during echocardiography and reversal flow in pulmonary veins. No extracardiac anomalies were present and for further evaluation we qualified only those cases with singleton pregnancies and delivery > 37 weeks of gestation.

Total of 18 cases were selected (0,76 %). One case resulted in termination of the pregnancy and in one case (twin pregnancy) was premature delivery, giving a total of 16 cases after prenatal diagnosis in our center and delivery with postnatal management in our institution (Prenatal Cardiology Center, High Risk Pregnancy Clinic, Neonatal Intensive Care Clinic, Pediatric Cardiology and Cardiac Surgery Department).

In our retrospective analysis we searched for perinatal

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and postnatal data in order to determine how our perinatal management can be improved. In order to answer this question the group of survivors was compared with the group of non-survivors.

Distributions of the qualitative variables were compared with Fisher exact test, and statistical characteristics of the quantitative variables with Mann-Whitney U test. Due to small size of the sample, frequencies of the qualitative parameters were presented as fractions and statistical characteristics of the quantitative variables as arithmetic means and 95% confidence intervals (95%CI). All calculations were performed with a Statistica 10 package (StatSoft, United States), with the threshold of statistical significance set at $p \leq 0.05$.

RESULTS

There were 10 non-survivors and 6 survivors (Table 1). In the group of non-survivors, in one case the medical history was incomplete, high risk factors were present in 5 out of 9 cases and in the group of survivors in 3 out of 6 cases (p 0,622).

High risk pregnancies were due to: 3 x miscarriages 4-7 months prior to current pregnancy, 1 x IVF (transfer of 5 embryos with reduction to 1, outside of Poland), 1x maternal mononucleosis in 1 trimester, 1 x maternal urinary tract infection, 1x appendectomy in first trimester and 1x family history with genetic syndrome (no further data available). None of the fetuses had increased nuchal translucency in the first trimester or abnormal Pappa test.

In the group of non-survivors there were 5 cases of HLHS and in the group of survivors 4 (the detailed cardiac diagnoses are provided in table 2.

We compared maternal age, BMI, fetal age during the last echocardiography before delivery, fetal heart size (HA/CA ratio), fetal heart size in transversal diameter (in mm), size of the foramen ovale in mm, pericardial effusion, amniotic fluid index (AFI), week of gestation during delivery, way of delivery, fetal/neonatal gender, neonatal birth weight and Apgar score, other anomalies, presence of other neonatal anomalies (such as anemia requiring blood transfusion before surgery), surgery up to day 10th and surgery after 11th day.

The only significant difference between survivors and non-survivors pertained to the fraction of newborns operated on up to 11th day, which was significantly higher among the survivors (5/6 vs. 2/8, $p=0.031$).

The cut-off value for the day of surgery (≤11 or 11 days) represents a median value for the whole set of data.

In the total group of 16 cases with restriction of the foramen ovale in majority the sex was male (Fig. 2).

None of the newborns presented cyanosis on the first day of postnatal life. All of them received prostin infusion without delay.

Parameter	Non-survivors (n=10)	Survivors (n=6)	p
Type of pregnancy:			
- high risk	5/9	3/6	0.622
- low risk	4/9	3/6	
CHD:			
- HLHS	5/9	4/6	0.545
- other	4/9	2/6	
Shunt:			
- yes	3/10	1/6	0.511
- no	7/10	5/6	
Other anomalies:			
- yes	5/10	3/6	0.696
- no	5/10	3/6	
PE:			
- yes	1/10	1/6	0.625
- no	9/10	5/6	
Delivery:			
- vaginal	5/10	2/6	0.451
- cesarean section	5/10	4/6	
Fetal gender:			
- male	7/10	6/6	0.214
- female	3/10	0/6	
Surgery up to 10th day:			
- yes	1/8	3/6	0.175
- no	7/8	3/6	
Surgery after 11th day:			
- yes	6/8	1/6	0.031
- no	2/8	5/6	
Anemia:			
- yes	2/10	(2/6)	0.489
- no	8/10	(4/6)	
Maternal age	28.3 (24-33)	26.6 (18-35)	0.622
BMI	27.3 (21-34)	33.2 (15-51)	0.355
Fetal age	35.0 (33-37)	37.2 (36-39)	0.125
HA/CA	0.34 (0.29-0.39)	0.39 (0.27-0.51)	0.392
AP	38.5 (32-45)	40.4 (32-48)	0.462
FO	3.7 (3.0-4.4)	3.0 (0.8-5.1)	0.372
AFI	10.5 (6-15)	15.5 (7-24)	0.183
Week of gestation	38.4 (38-39)	39.2 (37-41)	0.392
Birth weight	3052.2 (2866-3239)	3020. 0 (2565-3475)	0.738
Apgar score	9.0	9.0	0.907
Day of surgery	16.5 (11-22)	11.2 (6-16)	0.091

Table 1: Statistical characteristics of 10 survivors and 6 non-survivors with prenatal restriction of the foramen ovale

	Prenatal diagnosis	Cath lab	Surgery on day	Type of surgery	Demise	Day of discharge home
1	AS…progression to HLHS		7	Norwood stage 1		24th day
2	HLHS		14	Norwood stage 1	15th day	
3	APVS + LSVC	30rd day MAPCAS closure	53	Reconstruction of RVOT	54th day	
4	HLHS		11	Norwood stage 1		32nd day
5	AS…..HLHS	32nd day	9	Banding of RPA and LPA and 3 weeks later stent to PDA and FO		54th day
6	HLHS		12	Norwood	27th day	
7	SV IAA		11	Norwood		32nd day
8	HLHS		12	Norwood	40th day	
9	HLHS		11	Banding of RPA and LPA & stent to PDA and FO		42nd day
10	AS…HLHS	32	9	Banding of RPA and LPA and 3 weeks later stent to PDA and FO		54th day
11	Tricuspid atresia + TGA + Ao hypoplasia	3rd day Rashkind	No surgery		28th day	
12	HLHS		8	Norwwood		32nd day
13	AS….HLHS		9	Norwood stage 1	28th day	
14	HLHS	26th day Rashkind and stent to PDA	21 17	Banding RPA and LPA And 5 days later cath lab	60th day	
15	HLHS			Norwood stage 1	18th day	
16	HLHS		10	Norwood stage 1		At the age of 3 months still in the hospital undergoing dialysis due to renal insufficiency

Table 2: Prenatal echocardiography diagnoses in series of 16 fetuses with FO = or < 4 mm, reversal flow in pulmonary veins and harsh sound during fetal auscultation (all neonates after in utero transfer had diagnoses confirmed after delivery and prostaglandin administration after delivery with no delay) and their follow-up

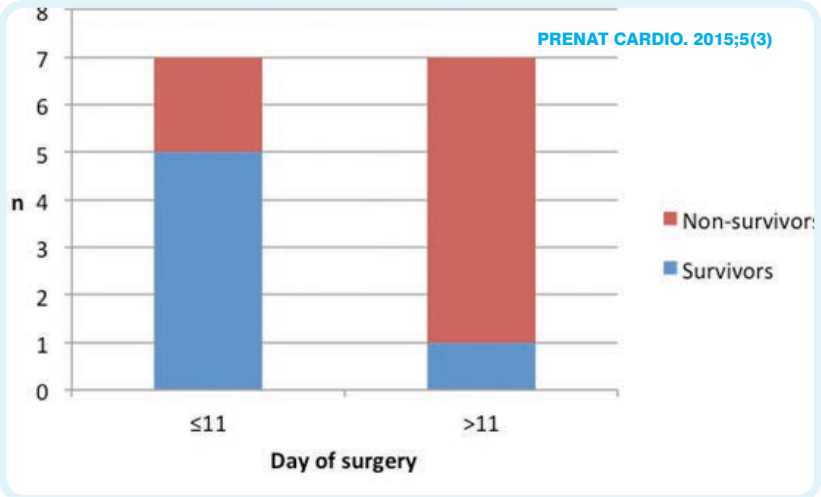

Figure 1: Fractions of survivors and non-survivors among fetuses operated on up to 11th day and after day 11th. The cut-off value for the day of surgery (≤11 or 11 days) represents a median value for the whole set of data.

The neonatal follow-up is presented in table 2. Only in one case (case nr 6: tricuspid valve atresia and transposition of the great arteries with aortic hypoplasia) Rashkind procedure was performed relatively early: on the 3rd day. Three days later the newborn presented renal insufficiency. No surgery was performed and he died on the 28th day after delivery. No other newborn was referred to the cath lab during the first week of postnatal life.

In ten neonates classic Norwood stage 1 was performed at mean 11th day +/3,6 (min. 7th day of postnatal life and maximum 14th day), in four cases hybrid surgery was performed (banding pulmonary branches and later on stent implantation into ductus arteriosus and foramen ovale; in one case there was reconstruction of the right ventricular outflow tract (absent pulmonary

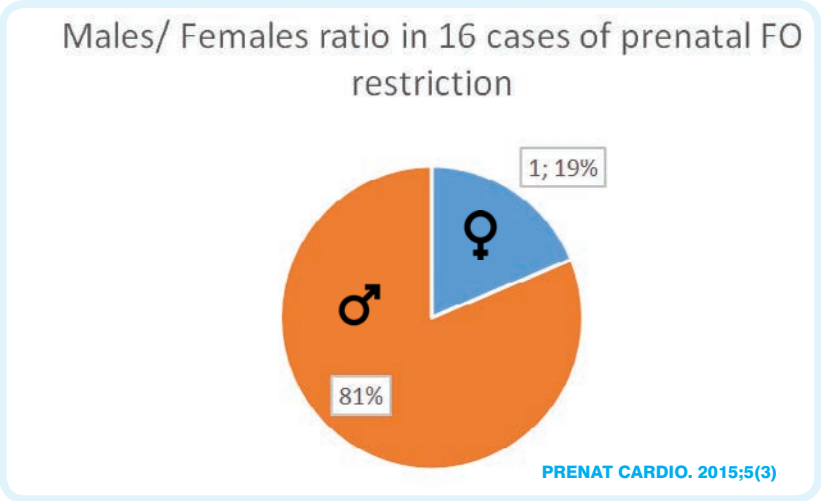

Figure 2: Male to female ratio in 16 cases of prenatal FO restriction

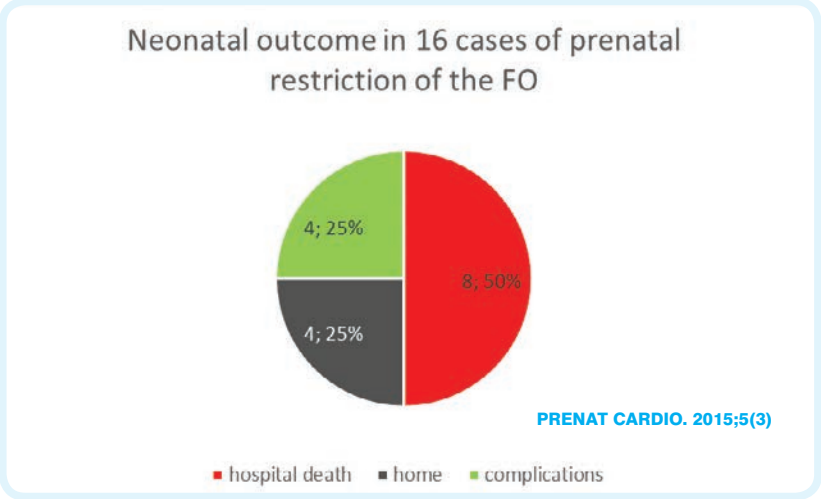

Figure 3: Neonatal outcome in 16 cases of prenatal restriction of the FO

valve) and in one case cardiac surgery was not attempted.

In one neonate with absent pulmonary valve syndrome reconstruction of the right ventricular outflow tract was performed which was preceded by major aortopulmonary collateral artery closure in cathether laboratory.

In one case no surgery was offered due to early kidney insufficiency and clinical status deterioration.

Among the 6 survivors 2 were discharged early from the hospital (at 24 and/ or 32 days of postnatal life) and four with prolonged hospital stay (54, 54 , 48 and 60 days).

In the 10 cases of non-survivors an autopsy was performed in 4 cases revealing pulmonary venous hypertension

DISCUSSION

Fetal circulation is different from that of the neonate. The placenta and umbilical cord, along with three natural connections, the ductus venosus, ductus arteriosus and foramen ovale that close after birth, play a significant role in fetal circulation.

The foramen ovale is a hole located within the interatrial septum that allows blood to flow from right to left atrium with the pressure gradient. The in-flow of blood into the right atrium includes oxygenated blood from the inferior vena cava, which is directed mainly (80%) to the left atrium through the foramen ovale[1].

Premature closure or restriction of the foramen ovale can occur at any point during pregnancy as an isolated defect within an anatomically normal heart[1,2,3,4] , or together with structural heart disease [5,6,7,8,9]. The cause of this phenomenon is not fully understood, according to the literature it has been associated with Parvovirus B19 infection[10], aneurysms of the atrial septum and intrauterine left ventricle thrombus [6,11]. It is the most common cause of fetal hydrops and right heart dilatation in a structurally normal heart[12]. Primary closure at early gestation is postulated to be responsible for hypoplastic left heart syndrome. It may also occur secondary to mitral atresia or critical aortic stenosis because of the increase in left atrial pressure [13]. The most common echocardiographic signs are right heart dilatation, hypermobile or redundant atrial septum.

Based on the literature there are different criteria for diagnosis of restricted foramen ovale: diameter less than 2.5mm, Doppler > 40 cm/s, foramen ovale/right atrial diameter < 0.3, foramen ovale/interatrial septum length <0,33 and foramen ovale/ascending aorta diameter<0,52[1,5,14,15,16,17,21] .

For the purpose of our research we accepted the size of the foramen ovale < 4 mm and blood flow > 70 cm/sec with typical hursh sound.

Premature closure or restriction of the foramen ovale as an isolated pathology is quite rare, for example it is registered no more than 3 times a year in the National Polish Registry of Fetal Cardiac Anomalies[4,18,19], and was identified in 23 of 1,682 (1.4 %) fetuses with structurally normal hearts by Uzun et al.[3]

Even though the prognosis is usually poor, especially in association with congenital heart disease[7,21] there are published cases in which premature closure or restriction of the foramen ovale had a good outcome[3]. Uzun et al retrospectively analysed 23 cases of restrictive foramen ovale, they concluded that prognosis remains good and pregnancy should not be discontinued as long as the hemodynamic status of the fetus remains stable, with no left-ventricular inflow obstruction, prolonged tachycardia, or congestive heart failure. However, they observed that restrictive foramen ovale is often concomitant with

extracardiac anomalies, persistent pulmonary hypertension in the neonate and therefore advise delivery at a tertiary center with proper neonatal care in order to exclude any previously undiagnosed systemic abnormalities in the neonate.

According to the prenatal classification of congenital heart defects [22] in our institution, which is based on the timing of intervention after delivery, we distinguish four groups. Group A comprises of "mild" heart defects that do not pose a threat to the life of the fetus or newborn and do not require intervention in the prenatal period or infancy. Group B are "severe" heart defects, without treatment these defects pose a threat to the neonate, they require intravenous prostin administration after delivery and elective cardiac intervention (for example HLHS with a broad FO, TGA with a wide FO, tricuspid atresia, complex heart defects with a single chamber, common truncus arteriosus, transposition of great vessels with a wide FO etc.)

Group C however comprises of "critical" heart defects which are life threatening to the fetus and newborn, we anticipate the need for urgent intervention, either before birth or immediately after delivery. In these cases, both due date and method of delivery (date and time of birth) must be agreed upon between the team of obstetricians, neonatologists, pediatric cardiologists in correspondence with the availability of the haemodynamic laboratory. This group also comprises of the most common ductal dependent defects but, unlike those in group B, require urgent intervention. This group includes: critical aortic stenosis, critical pulmonary stenosis, hypoplastic left heart syndrome with restrictive foramen ovale, transposition of the great arteries with a restrictive foramen ovale. In these cases, intervention is required in the first few hours after delivery. Finally group D including the most serious congenital heart defects.

It is in the heart defects which rely on atrial shunting that assessment of the foramen ovale is extremely important during prenatal life.[17] This is so fetuses that will require immediate intervention (group C) can be selected and distinguished from those that will not (group B).[23] According to the literature not only the direct assessment of the foramen ovale plays an important role in determining fetal hemodynamic status and but also pulmonary venous Doppler analysis [24,25] which in cases of critical left heart obstruction can be used to predict restriction of the atrial septum. Allison Divanović et al [24] concluded that fetuses with hypoplastic left heart syndrome a forward/reverse time-velocity integral ratio of 3 or less can predict the need for emergent atrial septostomy in the neonate. Histological findings in lung tissue of fetuses with the most severe form of HLHS and intact atrial septum show severely dilated lymphatic vessels and pulmonary vein arterialization, both indicators of pulmonary hypertension. This observation is also confirmed by our observation.

This rises the question- will intervention after delivery be too late in the most severe cases? A few centers across the world have attempted catheter relief of a restricted or closed foramen ovale.[26] Even though the technique is possible with minimal risk to the mother they do not give the expected results in the fetus. Kalish et al. from Boston [27] attempted to perform fetal atrial decompression via septal stent placement in nine fetuses with HLHS and intact atrial septum, with successful stent placement in four fetuses, but the clinical impact is yet to be determined and further study is necessary.

Our observations confirm the poor outcome in majority of fetuses with restriction of the foramen ovale, as only 4/16 had non-complicated perinatal outcome and survived after surgery.

Our data suggests the necessity for early neonatal surgery, with the statistical analysis of this series suggesting cardiac surgery no later than on day 10th. In our Cardiac Surgery Department not only newborns from this hospital after in utero diagnoses undergo treatment, but many others referred from the whole country, in majority without prenatal diagnosis, with no prostin infusion for transportation and in bad clinical condition. So paradoxically those newborns from "outside" in deep cyanosis and acidemia are sooner qualified for cardiac surgery compared with the stable neonate on prostin without deterioration after prenatal diagnoses.

Therefore our data from this research has crucial value which might help pediatric cardiologists and pediatric cardiac surgeons choose the candidates for early cardiac surgery and information from prenatal echocardiography about restriction of the foramen ovale should be taken into consideration as valuable information for the whole team of specialists, suggesting priority for cardiac surgery.

CONCLUSIONS

1) In the event of prenatal restriction of the foramen ovale early surgery by day 10th had a statistically better outcome in terms of survival compared to cases that underwent surgery at a later period at our Institute.

2) Prenatal restriction of the foramen ovale was more often related to male gender and in 75% of cases in our series had complicated follow-up: neonatal death or prolonged hospital stay.

3) Information from prenatal echocardiography regarding restriction of the foramen ovale should be taken into consideration as valuable information suggesting priority for early cardiac surgery

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