INTRODUCTION

APVS (Absent Pulmonary Valve Syndrome) is a rare disease and is often referred to as one of the variants of Tetralogy of Fallot. Its incidence in Poland, according to The Polish National Registry of Fetal Cardiac Pathology (ORPKP) in years 2004 – 2016 was 0.6%. This disease is caused by the absence or the residual pulmonary artery valve resulting in significant dilation of the pulmonary trunk and its branches. In utero deaths are reported. After birth, the major problem is respiratory failure and high perinatal and postoperative mortality.

MATERIAL AND METHODS

Our data set from 1995 to 2016 included eleven fetuses with APVS who were diagnosed in our unit, at the average 27.5 weeks of gestation (min. 18.5 - max. 37.1 weeks of gestation). Two groups were analysed in this series of cases: “Old one” by 2011 (n = 6) and “New one” since 2011 (n = 5) and perinatal care as well as survival were compared. We analysed the fetal echo results, perinatal care including transplacental digoxin and steroids treatment in NEW group, the longevity of the pregnancy and neonatal/infants outcome.

Results: In Old group, the average day of cardiac surgery was day 91st after birth (max. 161) and the survival was 50%. In the New group the average surgery day was 41st day and the postoperative survival was 60%, however there was no statistical significance (p > 0.05).

Conclusions: There is no single parameter from prenatal life in foetuses with APVS which may allow to predict the positive outcome meaning neonatal survival. However, optimal perinatal care (early detection of defect, transplacental digoxin at least 3-4 weeks, steroids, no preterm delivery, on-time delivery, postnatal care in tertiary center) and relatively early cardiac surgery may have combined impact on the improvement of survival after prenatal diagnosis of APVS, however more data are necessary to prove this hypothesis.

Key words: Absent pulmonary valve syndrome, survivability, surgery, prenatal echocardiography, monitoring
of gestation at the time of birth, the neonatal birth weight, Apgar score, day of surgery as well as the material used during the cardiac surgery (homograft, Contegra, CorMatrix, own tissue). For statistical analysis we used average, STD and Mann-Whitney U test.

**RESULTS**

The serie of 11 patients and their follow up is presented in Figure 1. The cardiac surgery material is presented in Fig. 2. The Old group and New group are presented in Table 1a and Table 1b and the comparison of several data is presented in Table 2.

In the first trimester of pregnancy – NT was elevated in one case (2.9 mm) in Old group, in five cases there were no 11-13 weeks examination performed, and in the other fetuses NT was within the normal range up to 2.5 mm. Ductus arteriosus was present in 3 cases, the VSD, accompanying the defect, also in three. In the Old group there were two deaths in utero, no terminations of pregnancies and two postoperative deaths. In the New group, there were no in utero deaths or terminations. In Old Group the first echocardiography examination was in 30.5 weeks and 24.6 in New group (Table 2, Fig. 2). The echocardiographic monitoring of fetal well-being was performed in our centre from the time of detection to birth: max. 6 times when the APVS was diagnosed at 20 weeks of gestation and min. 1 time when the APVS diagnosed at term. The Hai/Ca index in the Old group was on average 0.46, in the New group was 0.45. Tei index for LV in Old Group was 0.4 (mean) and 0.4 (mean) in New group. The transplacental digoxin treatment and the administration of steroids were performed in New Group. The mean gestational age at birth in Old group was 35.6 weeks and in the New group was 39.4 weeks. The mean birth weight was similar in both group: in Old group was 2,930 g, and in New group it was 2,857. In Old group there were all vaginal deliveries and in the New group there were 3 vaginal deliveries and two cesarean sections. Apgar score: in the Old group was: 8.3, and in the New group was 8. In three fetuses in New Group the amniocentesis revealed the microdeletion 22q11.2. The mean day of cardiac surgery in Old group was 91st day of postnatal life and 41st day in New group. Postoperative mortality was 50% in the Old group and 40% in the New group. The postoperative survival in Old group was 50% and 60 % in New group (Fig. 3 and 4, chart 1).

The data on the method and surgical material were obtained in 7 cases: in five cases there was created the valve cusp from the anterior wall of the pulmonary artery stump, in one case Matrix and in one case Contegra. Current follow-up data are observed in 5 living children. One child, after one year from birth, required another surgery RVOT correction with the use of Contegra, a child born in 2001 after 11 years required a valve replacement with the use of Matrix material. In three patients the right bundle branch block was preserved, one is missing the follow-up after first postoperative check-up.

**DISCUSSION:**

APVS is a disease with heterogeneous image and generally unfavorable prognosis. It is currently considered one of the variants of Tetralogy of Fallot, although in view of the outcome and the method of surgery it appears to be a distinct heart defect. The characteristic is the two-way flow in the MPA (Main Pulmonary Artery) being a sign of total regurgitation where PV (Pulmonary Valve) should be. For the first time postnatal APVS was described in 1847 by Chevers. The first reports on prenatal diagnosis of APVS were published nearly 150 years later (1989) by Fouron et al. By 2016 PubMed had 228 publications on this defect, but only 36 on prenatal. Most available literature concerned mainly single cases or multiple cardiopulmonary corrections. The mortality, which is still very high is mainly caused by hypoxemia, respiratory/circulatory failure. Most of the complications are related
### Table 1a

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Initials</th>
<th>Week of gestation at first fetal echo in our center</th>
<th>Week of gestation at the time of delivery</th>
<th>Birth Weight</th>
<th>Apgar score</th>
<th>Way of delivery</th>
<th>Day of surgery after childbirth</th>
<th>Day of postoperative hospitalization</th>
<th>Day of postoperative death</th>
<th>Karyotype</th>
<th>Preoperative intubation</th>
<th>Own breath – WO</th>
<th>Intubation</th>
<th>Number of days of postoperative intubation</th>
<th>Material / method of cardiac surgery correction</th>
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<td>2,990</td>
<td>97</td>
<td>3</td>
<td>i</td>
<td>v</td>
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<tr>
<td><strong>Summary; average, SD</strong></td>
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<td>Average: 32.8 SD: 7.9</td>
<td>Average: 35.6 SD: 4.7</td>
<td>Average: 2,93 SD: 400</td>
<td>Average: 91 SD: 60</td>
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### Table 1b

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<th>Week of gestation at the time of delivery</th>
<th>Birth Weight</th>
<th>Apgar score</th>
<th>Method of childbirth</th>
<th>Day of surgery after childbirth</th>
<th>Number of days of postoperative hospitalization</th>
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<th>Preoperative intubation</th>
<th>Own breath – WO</th>
<th>Intubation</th>
<th>Number of days of postoperative intubation</th>
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<tr>
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<tr>
<td><strong>Summary; average, SD</strong></td>
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<td>Average: 27.7 SD: 7.9</td>
<td>Average: 39.4 SD: 8.9</td>
<td>Average: 2,857 SD: 277</td>
<td>Average: 41.1 SD: 18</td>
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to the development of distal pulmonary arteries that surround the inner lung branches of the bronchial tree and subsequently the compression and underdevelopment of the cartilaginous apparatus causing the emphysema. In the early ’80s and ’90s as well as in the early 2000s, it was believed that the later surgery in the infancy, the higher the odds of a good postoperative prognosis in patients with APVS. Due to the fact that this is a very rare defect, the literature available so far has a small database of postoperative results, and in the last decade there were only six reports comprehensive publications based on the analysis of a dozen cases (12-52). The authors analyzed the width of the lung branch, the presence of DA (ductus arteriosus), the association of defects with chromosomal abrasions (usually di George syndrome), a type of modification of cardiac surgery. Since 2012 at Prenatal Cardiology Department in our Institute, as a routine in fetuses with cardiac disorders and cardiomegaly, poor myocardial contractility and whose Tei index (for left or right ventricle) is > 0.45: there has been performed the transplacental digoxin treatment and double course of steroid therapy: first at 28th week of gestation and another one, "late" at 34th week of gestation. Digoxin passes through the placenta to the fetal circulation, reaching 40-80% of the maternal serum concentration. Its positive inotropic effect has found its application in prenatal cardiology and has been successfully introduced to treat both tachyarrhythmia, fetal edema and other causes of congestive heart failure in fetuses. The widest research on the use of digoxin in utero therapy was developed in 2008 by Huhta’s team. In Poland,
for the first time, the influence of digoxin on tachyarrhythmia in the fetus was described by Respondek-Liberska in 2006. The current state of knowledge about the safe use of digoxin in fetuses and the development of prenatal echocardiography confirms what in 1982 the precursor of digoxin treatment in pregnant women, Kleinman wrote in his article citing the widespread use of this drug in any type of fetal cardiovascular failure. Eckersley’s 6 years observations in isolated cardiac defects, showed that mortality was significantly lower in children who were prenatally diagnosed earlier (12%) than those diagnosed late (29%). Most of the pregnancies with fetuses with heart defects should have vaginal deliveries in the third degree reference center however there is no direct translation into the follow-up of the newborns. There is a work in progress on the ideal material for reconstruction of the right ventricular outflow tract. In our tertiary center and Department of Cardiac Surgery, all available materials are used; the one obtained from the Cor Matrix extracellular matrix as well as Contegra or a homograft. The analysis of the method and material used for pulmonary valve replacement and right ventricular outflow and also the day of the surgery had no significant correlation with survival (Figure 5, Chart 1). Similar observations were made by Sierra et al.: in 88 patients with a homograft and 50 with Contegra; he found that both materials had statistically similar with postoperative effects in 7-year follow-up. In most available literature, the dependence on prognosis of APVS was not statistically significant, and to date there has been no clear answer to the question of what is the prenatal prognostic factor in survival of these patients after cardiac surgery.

Currently based on our own research, the most likely hypothesis seems to be, not as previously thought, the APVS type, type of material and method of cardiac surgical correction but preparation of the fetus for on-time delivery, transplacental treatment (Digoxin and steroids), transport in utero, neonatology care as well as the time of cardiac surgery. Our analysis suggested a higher percentage of postoperative survival in New group: but by Mann-Whitney U test p > 0.05, did not show statistical significance. Chen’s paper et al. analyzing 23 cases of APVS and postoperative survival found a correlation with the day of surgery after birth: the average day of surgery was day 15th and the early postoperative mortality was only in one case. This early cardiac surgical intervention seems to be justified in view of the need to relieve long-term
pressure on the narrowing of the bronchial tree and trachea in cases of APVS.27

CONCLUSIONS

Our analysis suggest that there is no single parameter from prenatal life in foetuses with APVS which may allow to predict the positive outcome meaning neonatal survival. However optimal perinatal care (early detection of defects, transplacental digoxin at least 3-4 weeks, steroids, no preterm delivery, on-time delivery, postnatal care in tertiary centre) and relatively early cardiac surgery may have combined impact on the improvement of survival after prenatal diagnosis of APVS, however further research is needed to prove this hypothesis based on the larger case series.

References


Division of work:

K. Zych-Krekora -fetal echocardiographer, first draft of the manuscript, collecting the follow-up’s f the cases, literature search
M.Krekora - obstetrician, statistical analysis, work with the manuscript
M. Kopala - cardiac surgeon, provider of the cardiac surgery details, work with the manuscript
M. Respondek-Liberska -fetal cardiologist, collecting cases, work with the manuscript, final version

Conflict of interest: The authors declare no conflict of interest

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