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Research paper

Fetal cardiac tumours in a referral prenatal cardiology centre – series of 37 cases with neonatal follow-up

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Abstract

Introduction: Fetal cardiac tumours are relatively rare findings. The aim of this research was to present the natural course in a series of 37 fetuses with cardiac tumours, who had fetal echocardiography performed and the pregnancies had been continued until term.
Material and methods: This was a retrospective analysis of 37 cases with prenatally detected heart tumour. The study group was divided into multiple- and single-tumour subgroups and into survivors versus non-survivors. The number of survivors in subgroups and the incidence of prognostic factors were compared by χ^2 test. The presence of additional cardiac anomalies, the way of delivery and neonatal follow-up was analysed. The literature (Pub Med) was reviewed.
Results: There was no statistical difference between the number of survivors in groups of single versus multiple tumours ($p > 0.05$). In group of non-survivors there was a higher incidence of bad prognostic factors detected prenatally: pericardial effusion, mitral regurgitation, and cardiomegaly ($p < 0.05$). The authors suggested a different way of perinatal care and counselling in multiple and single fetal heart tumours.
Conclusions: Fetal cardiac tumours in the majority of cases were rhabdomyoma, and in case of normal heart anatomy and normal intracardiac flow the short-term prognosis was good. Fetal single heart tumour with progression of its size in the third trimester may require early surgical resection, so delivery in a tertiary perinatal and cardiac surgery centre might be necessary. Pericardial effusion, mitral regurgitation, and cardiomegaly might implicate a worse prognosis in the case of fetal heart tumour. Fetal cardiac tumour may require a multispecialist team approach to benefit from early detection and diagnosis.

Key words: fetal cardiac tumour, prenatal echocardiography, algorithm, follow-up.

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Introduction

Fetal cardiac tumours are relatively rare in obstetricians' practice but are more commonly found in prenatal cardiology centres. According to the Polish Nationwide Registry of Fetal Cardiac Pathology, in the years 2004-2018 they occurred in 1.05% of our patients' fetuses. According to other data by Yu et al. and Yuan, the prevalence in their fetal population was lower (0.08–0.2%) [1–3].

Fetal cardiac tumours are often primary and benign tumours. The most prevalent are rhabdomyoma, fibroma, and teratoma or myxoma [4–7].

There are numerous reports on fetal cardiac tumours with significant numbers of terminations, so natural follow-up from our series is of very special value for counselling parents to be, especially if there is a decision to continue the pregnancy regardless of histopathology examination and genetic make-up.

Material and methods

This was a retrospective analysis of 37 cases of fetal cardiac tumours detected and referred to our unit between 1993 and 2018 (25 years). The computer database of our unit (FMaker Pro) was searched for "heart tumour", and the study group was divided into two subgroups: single or multiple tumours and, regardless of the tumour nature, into survivors versus non-survivors.

The fetal heart anatomy was described as normal or congenital heart defect. The presence of additional cardiac anomalies was analysed, such as: cardiomegaly, arrhythmia, mitral or tricuspid valve insufficiency, cardiac hypertrophy, and pericardial effusion. Also, extracardiac anomalies were extracted from the records, such as: polyhydramnios (AFI > 25), oligohydramnios (AFI < 10), small for gestational age according to biometry and last menstrual date, pyelectasis > 5 mm, presence of cysts abdominis, hydrops testis, ventriculomegaly, hydrothorax, situs inversus, and genetic syndrome.

The way of delivery and neonatal follow-up was analysed. The number of survivors in the group of single versus multiple tumours was compared by chi-square test with $p < 0.05$. Also, the pericardial effusion, cardiomegaly, and mitral regurgitation during fetal life in the group of survivors versus non-survivors was compared by chi-square test with $p < 0.05$.

The literature (Pub Med) from 1997 to 2018 was also reviewed to show the number of multiple versus single tumours, terminations of pregnancies, and cases who survived.

Results

Demographic data

Fetal cardiac tumours were detected between the 20th and the 40th week of gestation. On average, the diagnosis in our centre took place in the 28th week of prenatal life.

We observed annually one to four cases of this pathology. Sixty-five per cent of cases had single tumours (Figure 1) and 35% had multiple (Figure 2).

On average, two echocardiographic examinations were performed in each case (maximum, in case of early diagnosis, seven echocardiographic examinations were performed for fetus since detection of the tumour till labour).

In the group of multiple tumours, in 20 cases there was normal heart anatomy and in four cases there were additional heart defects, such as: common atrioventricular canal (AVC), aortic valve atresia + total abnormal pulmonary venous return (TAPVR), aortic valve stenosis, and ventricular septal defect (VSD).

In the group of single tumours, there were also additional extracardiac tumours: kidney tumour and lateral ventricle tumour (subependymal giant cell astrocytoma was diagnosed).

The coexistence of cardiac tumour and heart defect was comparable in both groups – 17.4% in the multiple-tumour group and 23% in the single-tumour group ($p = 0.066$, χ^2 test). Extracardiac malformations were also presented (Table 1).

Concomitant cardiac and extracardiac anomalies were much more prevalent in the single-tumours group 28/13 than in the multiple-tumour group 28/24 (Table 2). One case of multiple cardiac tumours was also diagnosed with Down syndrome.

Outcome data

Neonatal survival was higher in the multiple-tumour group (79%) than in the single-tumour group (54%), but without statistical significance ($p = 0.1434$, χ^2 test) (Figure 3).

Cases with single or multiple heart tumour who did not survive presented during the fetal life: pericardial effusion (4x),

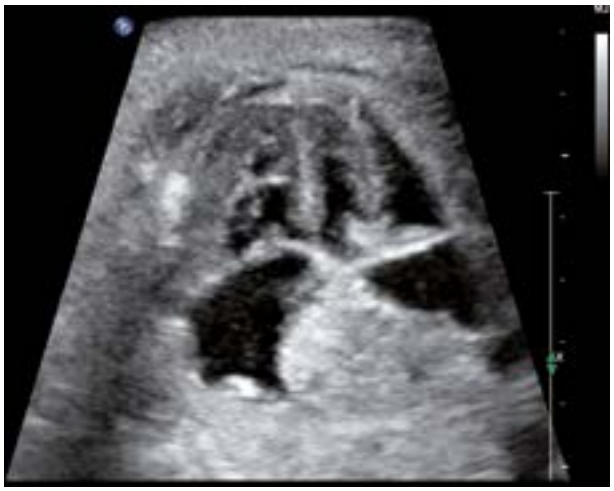


Figure 1. Single cardiac tumour

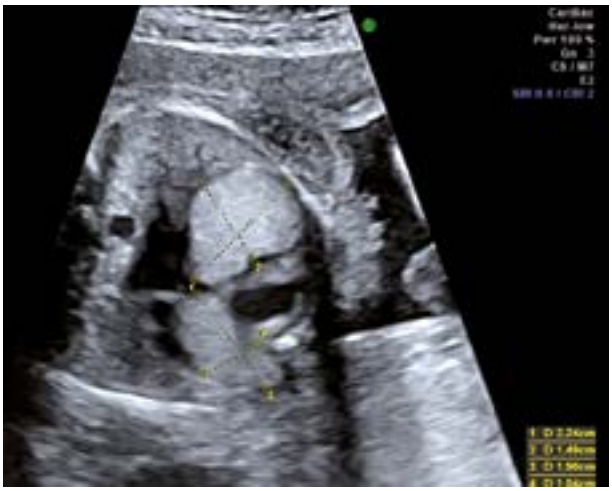


Figure 2. Multiple cardiac tumour

cardiomegaly (4x), small for gestational age (3x), mitral insufficiency (2x), tricuspid valve insufficiency (2x), myocardial hypertrophy (1x), arrhythmia (2x), hydrothorax (2x), congenital heart defect (2x), and polyhydramnios (1x) or oligohydramnios (2x) (Figure 4).

Non-survivors presented statistically significantly higher incidence of pericardial effusion, cardiomegaly, and mitral regurgitation during fetal life (χ^2 test, Table 3).

Two survivors with single heart tumours (teratoma and myxoma) had cardiac surgery on the third and sixth day of postnatal life with good outcome. The case with fibroma was operated on the second day and did not survive (eighth day).

The most common in both groups was postnatally confirmed rhabdomyoma – in 100% of multiple tumours and in 54% of single tumours. The other fetal cardiac tumours according to postnatal evaluation were: fibroma – 23% (n = 3), teratoma – 16% (n = 2), and myxoma – 7% (n = 1). Of 37 cases detected prenatally by echocardiography, the diagnosis was confirmed by autopsy and histopathology in 11 cases, i.e. 11/37 (30%).

Literature review

Review of literature relating to fetal cardiac tumours is presented in Table 4. In total 332 fetuses were reported, but follow-up was presented only in 219. From this subgroup there were 60 terminations of pregnancies (27.4%), 51 neonatal deaths (23.3%), and 108 survivors (49.3%).

Based on our data and literature review, the following algorithm was proposed for our multispecialist team (Figures 5 and 6), considering the differences in the management of pregnancy with multiple and single cardiac tumours. These differences involve the frequency of fetal echocardiographic examinations, but an individual approach in each case is always mandatory.

Parent counselling was also recommended. It should concern further procreative plans, taking into consideration histopathological diagnosis, cytogenetic diagnosis, and genetic consultations, and the first fetal echocardiographic examination for the next pregnancy we would suggest at no later than the 15th week.

Discussion

Fetal cardiac tumours are relatively rare anomalies in the general population, but in the prenatal cardiology centre we expect a few cases per year. They can cause haemodynamic changes, which may threaten fetal well-being or can even be fatal, unless monitored [8, 9]. Echocardiography remains the main tool for monitoring and early clinical diagnosis [10–13], although histopathology and genetics are still significant in the diagnosis and treatment of benign cardiac tumours [14, 15].

Histopathology is usually unavailable during prenatal life; hence, in prenatal cardiology another approach should be developed. Fetal cardiac tumours are generally divided into single or multiple.

Tumour size may significantly influence fetal haemodynamic state by blood flow disturbances or arrhythmias, which require treatment [16, 17].

Table 1. Coexisting congenital heart defects (CHD) and extracardiac malformations (ECM) in multiple and single cardiac tumours (n = 37)

Coexisting CHD/ECM	Multiple tumours n = 24	Single tumours n = 13
AV canal	1	0
Aortic valve stenosis	1	3
Aortic valve atresia, TAPVR	1	0
VSD	1	0
Kidney tumour	1	1
Lateral ventricle tumour	0	1
Total	n = 5	n = 5

Table 2. Anomalies in study group (n = 37)

Cardiac/extracardiac anomalies	Multiple tumours n = 24	Single tumours n = 13
Cardiomegaly	5	10
Arrhythmia	1	0
Mitral valve insufficiency	3	0
Tricuspid insufficiency	3	3
Cardiac hypertrophy	1	3
Pericardial effusion	5	6
Polyhydramnion (AFI > 25)	2	2
Oligohydramnios (AFI < 10)	1	2
Small gestational age	2	0
Pyelectasis unilateral (> 5 mm)	1	0
Cystic abdominis	1	0
Hydrops testis	1	0
Ventriculomegaly	1	0
Hydrothorax	0	1
Situs inversus	0	1
Down syndrome	1	0
Total	n = 28	n = 28

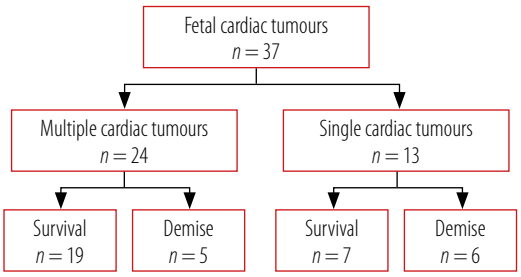


Figure 3. Fetuses with prenatally detected cardiac tumour – follow-up. Survival analysis – no statistical significance (χ^2 test, p = 0.1434)

When fetal cardiac tumour is detected in the middle of pregnancy during screening ultrasound performed by an obstetrician, the fetus should be referred to the referential centre of prenatal cardiology. Fetal monitoring should be planned, usually as an outpatient care, with appointments once per 3–4 weeks. More frequent appointments are needed after the 34th week of gestation – once per 1–2 weeks until labour.

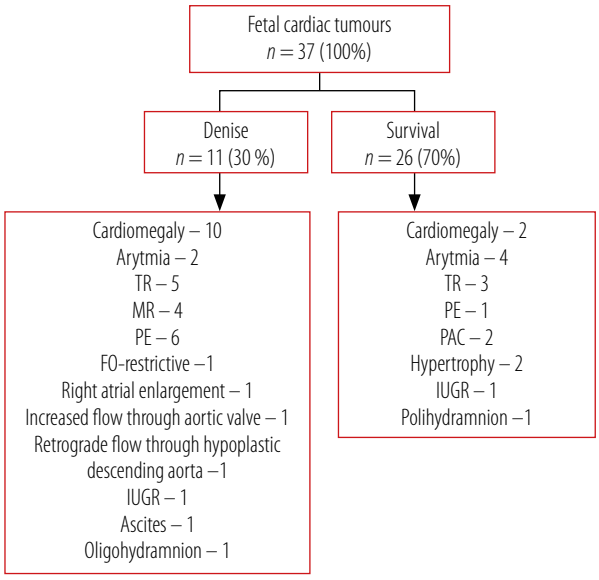


Figure 4. Symptoms of echo/sono in the fetal group cardiac tumours ($n = 37$)

Table 3. Comparison of additional anomalies during fetal life in survivors and non-survivors

Parameter	Survivors $n = 26$	Non-survivors $n = 11$	Difference (χ^2 test)
Pericardial effusion, *n* (%)	1 (4)	6 (55)	$p < 0.05$
Mitral regurgitation, *n* (%)	0 (0)	4 (36)	$p < 0.05$
Cardiomegaly, *n* (%)	2 (8)	10 (90)	$p < 0.05$

Multiple echocardiographic anomalies, such as cardiomegaly, pericardial effusion, and mitral regurgitation, should be considered as making the prognosis worse (Table 4).

Rhabdomyoma might be present in a familial occurrence manner, e.g. first-degree relatives, siblings, etc. [18, 19]. In selected cases of familial occurrence of rhabdomyoma, if the mutation is known, cytogenetic diagnostics should be proposed for pregnant women [15].

In the case of increasing circulatory failure, such as cardiomegaly, ascites, or pleural effusion, an attempt to improve myocardial contractility may be considered by transplacental digoxin treatment, but in our material of 37 cases, it was not necessary [10, 20, 21]. In cases of single tumours, which progressively increase their mass, in developing fetal circulatory failure, surgical treatment should be considered prenatally or in the first days of the newborn's life.

In the third trimester, MRI may be considered to exclude additional tuberous lesions in CNS or in the kidneys of the fetus [5, 22, 23].

Steroids should be considered from the 28th week of pregnancy in case of premature delivery suspicion, with polyhydramnios progression and lung immaturity. To prevent premature delivery, amnioreduction may be considered (usually after tocolytic therapy). In our material, two cases needed amnioreduction.

Cases of a progressive single cardiac tumour in the third trimester should be introduced to the team of cardiosurgeons prenatally. The team may decide to perform cardiac surgery in the first days after birth in the newborn (in our material five newborns were operated on the 2nd, 4th, 8th, 16th, and 32nd day). The team may also discuss conservative management.

In cases of inoperable fetal cardiac tumours, pharmacological treatment with mTOR inhibitors (sirolimus and everolimus) may be considered. The effects of pharmacotherapy, resulting in tumour remission, as well as improvement of fetal heart function with postnatal life extension, were described by Yuan [2], and MacKeigan and Krueger [24]. There are only single, casuistic reports so far, and the safety of such therapy is still open to doubt.

According to the literature, it is also possible to take a chance on surgical resection of growing fetal cardiac tumour [25–28].

Monitoring of fetal haemodynamic state, starting early and lasting for at least a few weeks, and comparison of assessments of fetal cardiovascular efficiency in the following weeks before the delivery facilitates the optimal decision of spontaneous labour or caesarean section. In our centre, caesarean childbirth constituted 65% of labours. Before delivery, one case needed repeated monitoring (seven ECHO examinations).

In the group of multiple tumours, CS constituted 58% of labours (14/24) and 77% (10/13) in the group of single tumours, and typically the decision was made by an obstetrician regardless of fetal haemodynamic state during the final weeks of gestation. The main tool for fetal monitoring just before delivery was CTG.

Single tumour or multiple tumours, which obstruct left ventricular outflow tract (LVOT) or right ventricular outflow tract (RVOT), may mimic critical heart defect. Intravenous umbilical rout for prostaglandin E1 infusion, just after delivery, is then indicated. Such a newborn requires further monitoring 24/7 in an intensive care unit. In our material, two newborns needed prostaglandin E1 infusion.

If there was no abnormality or defect of fetal thymus detected, the newborn might be vaccinated.

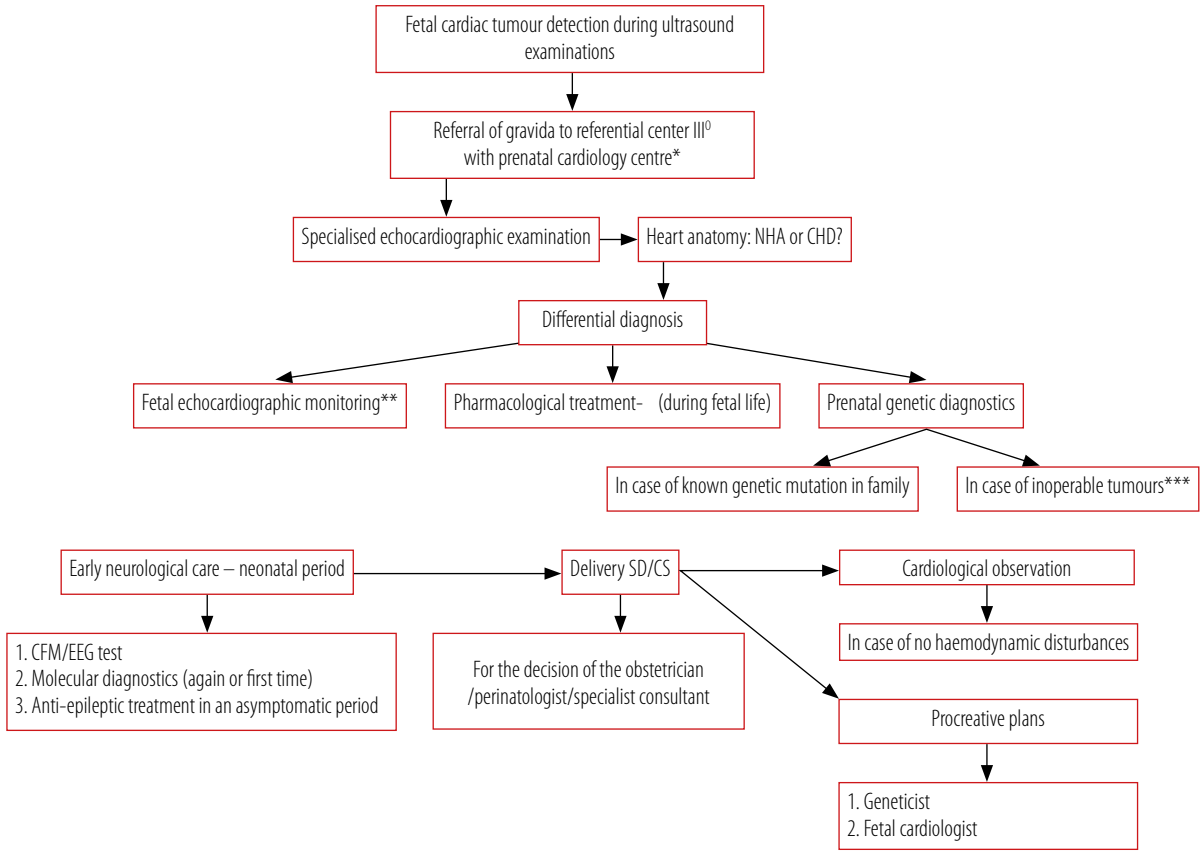
In the case of rhabdomyoma suspicion, we advocate early neurological control including EEG and molecular diagnostics, EPISTOP programme [29], Yates et al. [30, 31] and Jóźwiak et al. [32, 33].

Tuberous sclerosis is a heterogeneous genetic disorder, so prenatal diagnosis is possible only if a member of the family is diagnosed with causative mutation. The disease is mostly caused by TSC2 gene mutation (69%) and TSC1 gene mutation (26%), and in 5% of cases genetic mutation is not determined [34, 35]. The method of molecular diagnostics depends on the type of mutation present in the family.

Comparing our data with the observations of Yinon from 2010 and Chen from 2018, fetal and neonatal survival rates with single or multiple cardiac tumours were similar. The authors emphasised that the prognosis in the postnatal period depends primarily on neurological symptoms associated with tuberous sclerosis.

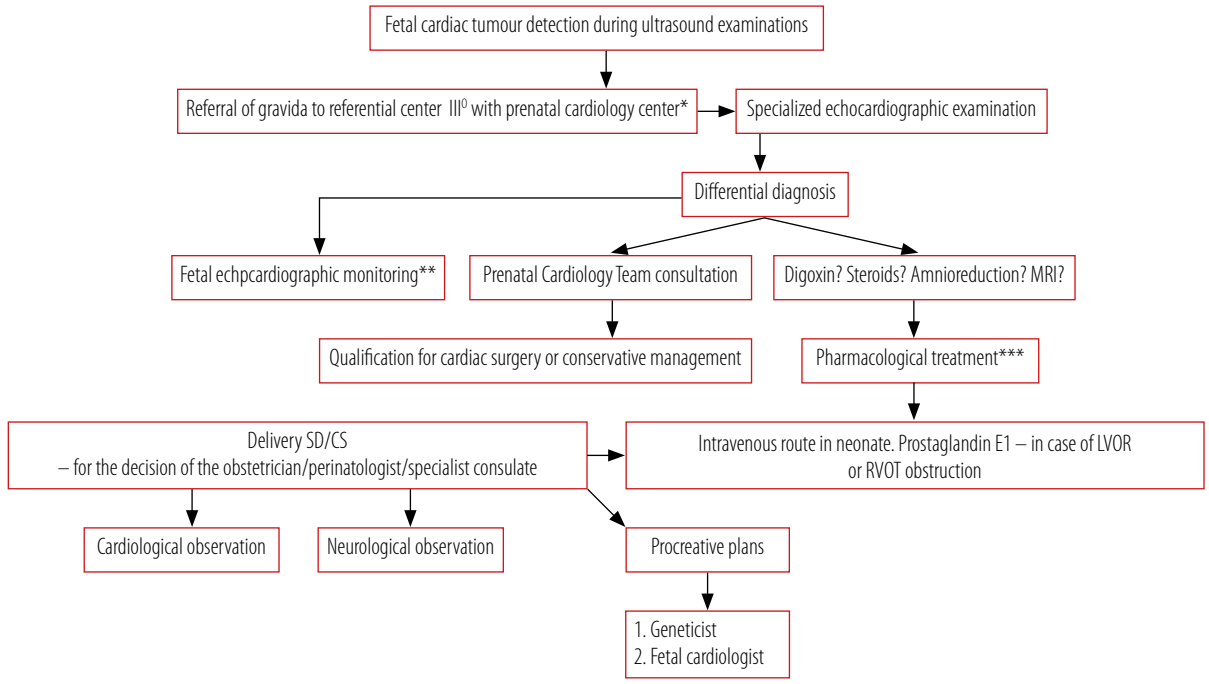
Table 4. Fetal cardiac tumours, literature review – last decade

First author	Article title, journal	Year	Number of cases	Multiple tumours	Single tumours	TOP	Newborn death	Number of survivors
Geipel A.	Perinatal diagnosis of cardiac tumours, Ultrasound Obstet Gynecol	2001	12	Rhabdomyoma ($n = 6$)	Rhabdomyoma ($n = 5$), fibroma ($n = 1$)	3	3	6
Gamzu R.	Evaluating the risk of tuberous sclerosis in cases with prenatal diagnosis of cardiac rhabdomyoma,Prenat Diagn	2002	18	6	12	No data	No data	No data
Isaacs H. Jr.	Fetal and neonatal cardiac tumours, Pediatr Cardiol	2004	89	Rhabdomyoma ($n = 57$)	Teratoma ($n = 20$), fibroma ($n = 6$), vascular tumours ($n = 6$)		No data	No data
Niewiadomska-Jarosik K.	Prenatal diagnosis and follow-up of 23 cases of cardiac tumours, Pediatr Cardiol	2004	23	12	11	0	9	14
Chao A.S.	Outcome of antenatally diagnosed cardiac rhabdomyoma: case series and a meta – analysis, Ultrasound Obstet Gynaecol	2008	11	6	5	1	4	6
Yinon Y.	Fetal cardiac tumours: a single-centre experience of 40 cases, Prenat Diagn	2010	40	Rhabdomyoma ($n = 25$), fibroma ($n = 1$)	Rhabdomyoma ($n = 8$), teratoma ($n = 3$), fibroma ($n = 2$), haemangioendothelioma ($n = 1$)	3	5	26
Pucci A.	Life-threatening tumours of the heart in fetal and postnatal age, J Pediatr	2013	12 (4 fetuses, 8 children)	–	Rhabdomyoma ($n = 6$), haemangiomas ($n = 3$), central fibrous body chondroma ($n = 1$), fibroma ($n = 1$), or left atrial myxoma ($n = 1$)	2	6	4
Yu Q.	Clinical value of prenatal echocardiographic examination in the diagnosis of fetal cardiac tumors, Oncolgy Letters	2016	8	6	2	5	1	2
Więckowska K.	Heart Tumours in 33 fetuses – review of twenty-two years of the single-centre experience, Prenatal Cardiology	2016	33	19	14	0	19	14
Żalińska A.	Single fetal cardiac tumours and follow-up based on 13 cases from the fetal cardiac referral centre in 1993-2017, Prenatal Cardiology	2017	13	–	13	1	4	8
Ide T.	Prediction of postnatal arrhythmia in fetuses with cardiac rhabdomyoma, J Matern Fetal Neonatal Med	2018	20	Rhabdomyoma ($n = 20$)	–	0	0	20
Chen J.	Fetal cardiac tumours: fetal echocardiography, clinical outcome, and genetic analysis in 53 cases, Ultrasound Obstet Gynecol	2019	53	37	16	45	0	8



*Incorporating: Imaging Department, Intensive Care Unit, Cardiology Department, Cardiosurgery Department, Neurology Department, **Once per 4, 3, 2, or 1 week. Depends on fetal hemodynamic status. Optimally, at least once per 4 weeks; after 34th week of gestation – at least twice per week, ***After Prenatal Cardiology Team consultation, in the case of treatment with mTOR inhibitors, cardiomegaly, asystole, etc.*

Figure 5. Suggested healthcare algorithm for management of multiple fetal heart tumours



*Incorporating: Imaging Department, Intensive Care Unit, Cardiology Department, CardiosurgeryDepartment, Neurology Department, **Depends on fetal hemodynamic status and gravida's age. Optimally, at least once per 2 weeks; after 34th week of gestation- at least once per week. After 38th week of gestation gravida should be admitted to Obstetrical Department for continuous fetal echocardiographic monitoring, ***Folic acid supplementation.*

Figure 6. Healthcare algorithm for management of fetal single cardiac tumour

In our prenatal and perinatal healthcare algorithm proposal of fetal single or multiple cardiac tumours we also included principles of gravida and her family consulting regarding future procreative plans. Full genetic consultation in the procreative aspect is possible only if molecular mutation is identified and determined. Thus, in the case of rhabdomyoma suspicion without significant family history, fetal or neonatal samples should be taken and tested on TSC1 and TSC2 gene mutation in a referential centre, in which the Next-Generation Sequencing technique (NGS) is available. The first neurological consultation of the newborn with prenatal diagnosis of cardiac tumour is indicated after birth and before discharge from hospital.

The first paediatric cardiologist consultation of the newborn/ infant with cardiac tumour is recommended in its 3rd–4th week, after discharge from hospital, as outpatient care. In the case of fetal cardiac tumours, we recommend echocardiographic examination for close family members.

Because in the current literature it is easier to find information about termination of pregnancies [36] than about natural follow-up, we believe that the presented data from our centre should be known to the medical society.

Conclusions

Fetal cardiac tumour in the majority of cases was rhabdomyoma, and in cases of normal heart anatomy and normal intracardiac flow, the short-term prognosis was good; however, parents need to be informed about possible multiple sclerosis in the future.

Fetal single heart tumour with progression of its size in the third trimester may require early surgical resection, so delivery in a tertiary perinatal and cardiac surgery centre might be important.

Pericardial effusion, mitral regurgitation, and cardiomegaly might implicate worse prognosis in case of fetal heart tumour.

Fetal cardiac tumour may require a multispecialist team approach to benefit from early detection and diagnosis.

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Conflict of interest

The authors declare no conflict of interest.

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