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Fetal teratomas – A retrospective observational single-center study

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Abstract

Objective: Evaluation of course and outcome of pregnancies with prenatally diagnosed fetal teratomas of various locations in a single center between 2002 and 2019.

Methods: Retrospective observational single-center study including prenatally suspected or diagnosed fetal teratomas. Focus was put on ultrasound findings during pregnancy. Complications, need for intervention and outcomes were compared according to tumor location.

Results: 79 cases of fetal teratomas were seen at our center between 2002 and 2019. Most frequent tumor locations were the sacrococcygeal region (59.5%), neck (20.2%) and oropharynx (7.6%). Complications mainly included polyhydramnios and cardiac compromise. Need for intervention during pregnancy was significantly higher in pericardial teratomas. Preterm birth before 37 and early preterm birth before 32 weeks occurred in 72.7% and 29.1%, respectively. Major causes of perinatal death were tumor bleeding in sacrococcygeal teratomas (SCTs) and respiratory failure in cervical and oropharyngeal teratomas.

High cardiac output failure

Conclusion: There is a high need for intervention in pregnancies complicated by fetal teratomas. Pericardiocentesis in pericardial teratomas is often inevitable to reduce the risk of intrauterine demise. Amniotic fluid drainage in associated severe polyhydramnios helps to reduce the risk of preterm birth, a major cause of additional morbidity and mortality. MRI in supplement to prenatal ultrasound is useful in fetal teratomas of the neck and oropharynx in order to plan delivery.

1 | INTRODUCTION

Fetal tumors are rare. However, growing knowledge and better imaging technologies lead to increasing rates of prenatal diagnosis. Teratomas account for the majority of fetal tumors and are formed by pluripotent cells of all three germ cell layers (entoderm, ectoderm and mesoderm).[1] Usually, these predominantly benign tumors are located somewhere in the midline of the body, the most frequent locations including the sacrococcygeal region, the neck and the oropharyngeal cavity (where they are called "epignathus"), followed by less common locations such as the brain, pericardium, mediastinum, abdomen or testes. Diagnosis is usually made in the second or third trimester of pregnancy by ultrasound, where they appear as masses of mixed echogenicity with cystic and solid parts, calcifications and blood perfusion of varying degree. Typically, they are not associated with abnormal genetic findings.[2]

Time of diagnosis as well as prognosis of fetal teratomas depend on factors like tumor location, size and growth velocity. Associated

pregnancy complications may request intrauterine treatment options, such as amniotic fluid drainage, intrauterine blood transfusions and up to percutaneous radiofrequency ablation (RFA), pericardiocentesis or even fetal surgery.[3,4] The present study is a single-center study reporting on the diagnosis, management and outcome of prenatally diagnosed fetal teratomas of various locations.

What's already known about this topic

- Fetal teratomas account for the majority of fetal tumors. Course of pregnancy, outcome and individualized management mainly depend on tumor location.

What does this study add?

- Fetal airway passage in cervical and orofacial teratomas should be evaluated by ultrasound and supplementary MRI. Pericardiocentesis in fetal pericardial teratomas is a successful therapy in order to increase survival and prolong pregnancy. Minimal invasive treatment of SCTs with cardiac compromise remains a challenge.

2 | METHODS

This was a retrospective observational study including the data of more than 59.000 pregnancies booked at our tertiary level referral center of Obstetrics and Prenatal Medicine in Bonn, Germany, in the period between January 2002 and June 2019. Referrals to our center represent a mixed low- and high-risk population and are sent for targeted ultrasound examination or evaluation of suspected fetal anomalies. Thus, the majority of cases were sent with the presumed diagnosis of a tumor or fetal hydrops. All women received a detailed fetal anomaly scan including fetal echocardiography using high-resolution ultrasound equipment. Fetal teratoma was suspected based on the typical tumor-specific sonographic appearance and the location of the lesion in context with typical associated ultrasound findings. Extensive multidisciplinary counseling included information on natural course of the disease, the spectrum of antenatal complications and the pre- and postnatal management options.

We reviewed our data on the course of pregnancy and the development of complications (i.e. cardiac compromise, polyhydramnios and intrauterine death) with specific focus on tumor location. Prenatal intervention was offered for various reasons in complicated pregnancies (i.e. suspected anemia, cardiac compromise or fetal hydrops, prevention of preterm birth, cyst drainage prior to delivery to prevent rupture and bleeding). According to the *Fetal Cardiovascular Profile Score for the Assessment of Fetal Ventricular Dysfunction* cardiac compromise was defined as cardiomegaly, increased cardiac output, a reversed a-wave in the ductus venosus, or a combination of these findings with or without hydrops.[5]

For each case, outcomes were obtained from our perinatal database, neonatal records or autopsy findings. Perinatal survival and, when available, long-term outcome were compared in different groups of tumor locations. Some of the cases included in this study have been reported previously.[6,7]

The research ethics board of Bonn University Hospital approved the study (ID #249/19).

3 | RESULTS

Between January of 2002 and June of 2019, 59.421 patients were seen at our institution. Of them, 79 fetuses were diagnosed with teratoma, which gives an incidence of 1.3 in 1000 pregnancies in our cohort. Overall, there was a female-to-male ratio of >2:1 (55/79 females – 69.6%). After further subdivision into groups according to tumor location, a female-to-male ratio of 1:1 in teratomas of the neck, oropharynx and mediastinum, of 2:1 in teratomas of the pericardium and the brain and a female-to-male ratio of 4.2:1 in sacrococcygeal teratomas (SCT's) were seen.

Tumor location as well as time of diagnosis is shown in Table 1.

Karyotyping was not part of the routine diagnostic management but had been performed in 9 cases (all with normal results) prior to referral. There were no cases of postnatal karyotyping.

Fetal MRI was performed in order to gain more information on airway anatomy, tumor expansion and to plan delivery in fetuses that were diagnosed with either cervical teratoma, epignathus or teratoma of the brain (n = 9). In the six children with cervical teratoma we performed additional MRI mainly in order to assess feasibility of intubation. Uninterrupted airway passage was predicted by MRI in four cases, but was incorrect in one of them. In the remaining two cases, MRI was helpful to secure the bad forecast of prognoses, resulting in the decision of TOP and palliative care, one of each.

Certain tumor locations were associated with specific complications and ultrasound findings during pregnancy (Table 1, Figure 1). Polyhydramnios was associated in 50% of cases, most frequently in face and neck tumors and in pericardial teratoma. All cases with pericardial and mediastinal teratoma as well as 45% of SCT cases suffered from cardiac compromise, while fetal anemia was the third most frequent complication in fetuses with SCT (30%, Figure 1).

Miscellaneous prenatal interventions were necessary i.e. to prevent preterm birth, release cardiac tamponade or for tumor decompression prior to birth (Table 1).

There was termination of pregnancy (TOP) in 25.3% (n = 20/79), intra-uterine death (IUD) in 3.8% (n = 3/79) and 55 infants were born alive (69.6%, Table 1). One case of SCT was lost to follow-up. Mode of delivery and gestational age at birth are shown in Table 1. EXIT procedure (ex utero intrapartum treatment) was performed in five children: four with cervical teratoma and one with epignathus.

Preterm birth <37 + 0 weeks occurred in 40/55 (72.7%), and < 32 + 0 weeks in 16/55 (29.1%) cases, respectively. Average gestational age at delivery was not different with regard to tumor location.

Neonatal death occurred in 27.3% (n = 15/55). Postnatal mortality was highest among newborns with SCT and cervical teratoma.

TABLE 1 Characteristics of fetuses with tumors diagnosed prenatally (n = 79)

Tumor location	GA at diagnosis (weeks, mean [range])	Ultrasound findings	Prenatal intervention	GA at delivery[a]	Mode of delivery[a]	Outcome
All (79)	24 + 0 (12 + 6–36 + 6)	Cardiac compromise (32)MCA Vmax >1,5 MoM (16)Polyhydramnios (40)	AFD (18)EXIT (5)RFA (3)IUT (3)Tumor puncture (9)Pericardiocentesis (3) FETI (2)Ascites puncture (2) Ventricular drainage (1)	34 + 0 (25 + 3–41 + 5)	VB (7)CS (48/50)[b]	TOP (20)IUD (3)NND (15)[c]AAW (40)No follow-up (1)
Sacrococcygeal region (47)	22 + 3 (12 + 6–35 + 2)	Cardiac compromise (21)MCA Vmax >1,5 MoM (14)Polyhydramnios (18)	AFD (7)RFA (3)IUT (3)Tumor puncture (7)Ascites puncture (2)	33 + 2 (25 + 3–39 + 6)	CS (35)VB (1)	TOP (9)IUD (1)NND (6)AAW (30) No follow-up (1)
Neck (16)	23 + 5 (13 + 3–32 + 0)	Cardiac compromise (5)MCA Vmax >1,5 MoM (1)Polyhydramnios (12)	AFD (5)EXIT (4)Tumor puncture (2)FETI (2)	34 + 0 (30 + 0–38 + 2)	CS (9)[b]VB (1)	TOP (7)NND (6)AAW (3)
Oropharynx (6)	27 + 4 (21 + 1–36 + 5)	Polyhydramnios (5)	AFD (3)EXIT (1)	35 + 2 (30 + 4–37 + 4)	CS (3)[b]VB (1)	TOP (2)IUD (1)NND (1)AAW (2)
Brain (3)	32 + 6 (30 + 1–35 + 6)	Cardiac compromise (1)Polyhydramnios (1)	Ventricular drainage (1)	35 + 5 (33 + 5–37 + 4)	VB (2)	TOP (1)NND (2)
Pericardium (3)	30 + 2 (25 + 0–33 + 6)	Cardiac compromise (3)MCA Vmax >1,5 MoM (1)Polyhydramnios (3)	AFD (3)Pericardiocentesis (3)	35 + 0 (34 + 0–36 + 2)	CS (3)	AAW (3)
Abdomen (2)	30 + 3, 36 + 6	-	-	40 + 2, 41 + 5	VB (2)	AAW (2)
Mediastinum (2)	22 + 1 (19 + 6–24 + 3)	Cardiac compromise (2)Polyhydramnios (1)	-	-	-	TOP (1)IUD (1)

Abbreviations: AAW, alive and well; AFD, amniotic fluid drainage; AV, atrioventricular valve; CS, cesarean section; EXIT, ex utero intrapartum treatment; FETI, fetal endoscopic tracheal intubation; GA, gestational age; IUD, intrauterine death; IUT, intra-uterine transfusion; NND, neonatal death; RFA, radiofrequency ablation; TOP, termination of pregnancy; VB, vaginal birth; Cardiac compromise = cardiomegaly + av-valve insufficiency + hydrops.

[a]In live-born children >24 weeks of pregnancy.

[b]48 CS in live born children, 2 CS in stillborn children (1 case of cervical teratoma, 1 case of epignathus).

[c]Palliative care in 4 cases: 1 case of epignathus, 1 case of cervical teratoma, 2 case of fetal brain teratomas.

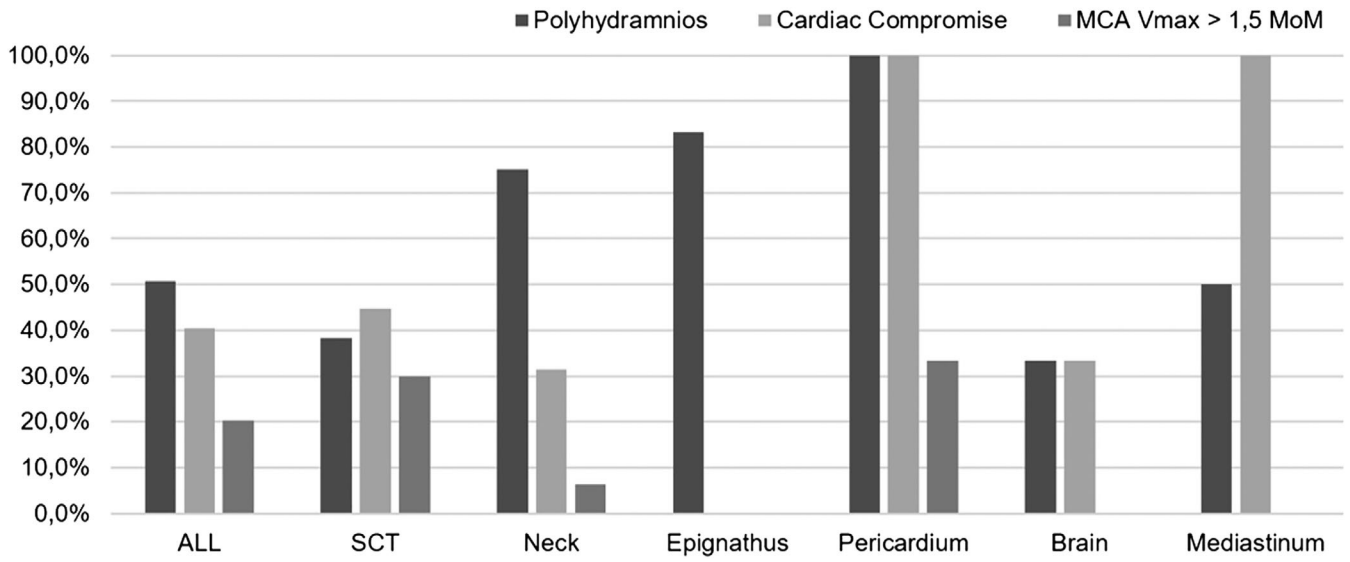

FIGURE 1 Pregnancy complications/Ultrasound findings according to tumor location in fetal teratomas. MCA Vmax, peak systolic velocity of the middle cerebral artery; MoM, multiples of the median; SCT, sacrococcygeal teratoma

TABLE 2 Long-term outcome of surviving children with teratoma (*n* = 40)

Tumor location	Range of follow-up Sex ratio	Therapy	Histology	Long-term sequaelae
Sacrococcygeal region (30)	1 month–15 years 22 ♀, 8 ♂	Complete tumor resection (25) Tumor resection, R1 or R2 (5) Additional chemotherapy (1) Plastic surgery for scars (3)	Mature teratoma[a] (17) Immature teratoma[b] (10) Immature teratoma with yolk sac tumor foci (3)	Bothering scars (3) Neurogenic voiding and defecation dysfunction (1) Associated malformations (3) VP-Shunting for hydrocephalus (1)[d]
Neck (3)	20–85 months 2 ♀, 1 ♂	Complete tumor resection (3)	Immature teratoma[b] (3)	Hypothyreosis (2) Local nerve damage (2) Arterial hypertension (1) VP-Shunting for hydrocephalus (1)[d]
Oropharynx (2)	30 months–7 years 1 ♀, 1 ♂	Tumor resection, R1 + plastic reconstruction (1) Complete tumor resection + cleft and dental surgery (1)	Mature teratoma[a] (2)	Cerebral venous sinus thrombosis (1) DPG-Syndrome (1)
Pericardium (3)	4 months–14 years 2 ♀, 1 ♂	Tumor resection, R2 (1) Tumor resection, R1 (2)	Mature teratoma[a] (2) Immature teratoma[b] with yolk sac tumor foci[c] (1)	-
Abdomen (2)	1.5 months–47 months 1 ♀, 1 ♂	Complete tumor resection (2)	Mature teratoma[a] (1) Immature teratoma[b] (1)	-

Abbreviation: DPG-Syndrome, Duplication of the Pituitary-Gland Syndrome.
[a]G0, according to the grading system by Gonzales-Crussi *d*.[8]
[b]G1 or G2.
[c]Chemotherapy was recommended but denied by the parents.
[d]VP-shunting in post-haemorrhagic hydrocephalus as a consequence of preterm birth.

Major causes were bleeding in SCT (6/36 livebirth, 16.7%) and hypoxia due to impaired intubation and ventilation in cervical teratoma (5/9 livebirth, 55.6%). In 4 newborns (2 brain teratomas, 1 epignathus, 1 cervical teratoma) the parents went for palliative care due to unfavorable prognosis.

Survival beyond the neonatal period was 72.7% (40/55; range of follow-up: 1 month to 15 years). All children with pericardial and abdominal teratomas survived. Long-term survival in SCTs, cervical as well as oropharyngeal teratomas was 83.3% (*n* = 30/36), 33,3% (*n* = 3/9) and 66.6% (*n* = 2/3), respectively.

Long-term outcome of survivors is given in Table 2. Complete tumor resection was achieved in all cases of neck and abdominal teratoma and in 77.5% (n = 31/40) of the total group. Histology showed mature teratoma in 55% (n = 22/40), immature teratoma in 35% (n = 14/40) and immature teratoma with yolk sac tumor in 10% (n = 4/40).

4 | DISCUSSION

Fetal teratomas are rare.[9,10] The reported incidence is between 0.07 and 2.8 in 1000 pregnancies,[2,10,11] in accordance to our study (1.3 in 1000).

Ultrasound findings, pregnancy complications, need for intervention as well as prognosis strongly depend on tumor location.

Similar to other studies[1,2,11] the most frequent tumor location was the sacrococcygeal region. In fetuses with SCTs, associated structural abnormalities can be found in 11%–38% and may include concomitant sacral defects and anorectal malformations.[12] Occasionally, bladder obstruction secondary to local tumor growth may require intra-uterine shunting. Tumor size, solid fraction and vascularization are major determinants of prognosis.[13,14] Large, solid and highly vascularized tumors increase the risk of arteriovenous shunting and high cardiac output failure. Intratumoral bleeding may aggravate cardiac compromise.[15–17] For the latter cases intrauterine treatment via RFA,[18–20] in-utero tumor resection[21,22] or open fetal surgery have been reported. RFA was applied to three fetuses in our series, but did not have the desired success. A recent small case series of minimal-invasive treatment with review of the literature suggested some improvement in perinatal outcomes of fetuses with solid SCT and hydrops, but the number of intrauterine death and preterm birth was high.[23] Perinatal mortality was 35% in our collective, which is consistent with the literature.[24]

Polyhydramnios was the leading pregnancy complication of neck tumors. Cesarean section combined with fetal endoscopic tracheal intubation (FETI), ex-utero intrapartum treatment (EXIT) or operation on placental support (OOPS) involving multidisciplinary teams is essential to provide safe airway management. Fetal MRI has been suggested to provide additional information on airway anatomy.[25–27] Our experience shows that prenatal MRI is a complementary tool, but, nevertheless, is not error-free. Yet we believe fetal MRI should be offered to all patients with cervical teratoma in order to optimize peripartum management.

Epignathus arise from the fetal palate or pharynx, fill the buccal cavity and usually protrude from the mouth. Intracranial tumor extension can severely worsen prognosis, thus detailed fetal neurosonography as well as additional fetal MRI is recommended.[25,28] In our cohort, one child was diagnosed additionally with duplication of the pituitary gland (DPG) syndrome.[29] Epignathus is found in 16% of children with this rare diagnosis.

Pericardial teratomas account for 9.5%–19% of all fetal primary cardiac tumors[30–34] and are almost always associated with pericardial effusion.[6,35–37] As we[6] and other studies have shown before, fetal pericardiocentesis is often inevitable in order to prevent cardiac tamponade and fetal hydrops.[35,38,39] Successful intrauterine tumor resection[35] as well as pericardio-amniotic shunting as an alternative to serial pericardiocentesis[40] have been reported, however, remain exclusive. Postnatal tumor resection is the treatment of choice and delivers good results.[41] Little can be found on the subject of incomplete vs. complete tumor resection. Despite the incomplete removal, follow-up of all three children in our series is uneventful so far. Regardless, regular check-ups should be pursued since tumor recurrence even after years has been described.[42]

Teratomas of the brain are very rare, but account for the majority of fetal intracranial tumors. They are usually diagnosed in late second or third trimester and often lack associated ultrasound findings. Their prognosis remains very poor with survival rates <10%.[43]

Fetal mediastinal teratomas often cause second trimester non-immune hydrops, therefore prognosis is rather poor.[44–50] In our series, post-mortem histological examination identified immature mediastinal teratoma in one case, which is more rare, tend to grow faster and thus lead to hydrops quicker.[48] In case of smaller tumors or lacking compression of mediastinal organs, prognosis might be better.[51] Reported treatments include in-utero tumor puncture in cystic lesions,[52] in-utero tumor resection[51] as well as EXIT-procedure[45] and postnatal tumor surgery.

Intraabdominal teratomas are usually discovered postnatally.[1] Differential diagnoses include ovarian or mesenterial cysts, liver hemangiomas,[53] fetus-in-fetu[53–56] as well as testicular teratoma as in our study. Long-term outcome after tumor resection is usually very good.

Strengths of our study is the high number of cases with a meticulous intrauterine and postnatal follow-up. Aside from the general limitations of retrospective studies, the specific limitations of our study include small numbers in certain tumor location groups which prevent further statistical analysis and the restrictions associated with a tertiary referral center which tend to see more severe cases and may therefore have higher rates of TOP as well as lower overall survival.

In conclusion, in order to achieve best outcome for children with teratomas, it is important to recognize specific complication patterns during the course of pregnancy and to meet them with a multidisciplinary approach.

Need for intervention is high throughout gestation and ranges from fetal pericardiocentesis, to amniotic fluid drainage, or cyst puncture in order to facilitate delivery. Experience with successful minimal-invasive treatment in cases with high cardiac output failure still remains limited. Additional imaging by MRI should be considered in particular in tumors of the neck and oropharynx, however, is not in general superior to prenatal ultrasound, which offers very high sensitivity in the diagnosis and spatial extension of fetal teratomas.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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