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INTEGRATED STUDY MASTER'S THESIS

Fetal Teratomas

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Abbreviations

- AFI = Amniotic fluid index
- AFP= Alpha-fetoprotein
- BFFE = Balanced fast-field echo
- EXIT Surgery = Ex Utero Intrapartum Treatment Surgery
- HF =Heart failure
- MCA-PSV= middle cerebral artery-peak systolic velocity
- MRI= Magnetic Resonance Imaging
- PI = Second-trimester uterine artery pulsatility Index
- RFA = Radio-frequency thermal ablation
- SAR = Specific absorption ratio
- SCT = Sacrococcygeal Teratoma
- SDP = Single deepest pocket
- SSFSE = Single-shot fast spin echo
- TEDI = Tracheoesophageal displacement index
- TFR = Tumor-volume-to-fetal-weight ratio
- T1WI = T1-weighted imaging
- US = Ultrasonography
- W/kg = Watts per kilogram

Summary

Fetal teratoma is a rare condition. Yet it is the most common type of fetal tumor. It is derived from all three germ layers and can have solid or cystic morphology. Fetal teratomas are usually benign, though in some cases they can be malignant. The most common type of Fetal teratoma is sacrococcygeal teratoma.

The diagnosis is usually done by ultrasonography during the second trimester. Magnetic resonance imaging can then aid in the diagnosis of fetal teratomas. Surveillance of the maternal and fetal

condition is one of the most important treatment strategies during the pregnancy period. Frequent check ups by specialised healthcare providers are crucial for a positive pregnancy outcome. Treatment involves intrauterine surgery, EXIT to resection or postnatal removal of the teratoma. Follow up is needed as a small percentage of fetal teratomas become malignant over the course of the patient's life.

Due to the rare occurrence of fetal teratomas research especially new and updated research is not abundantly available. Most of the research available at the moment is composed of case reports. Treatment strategies are still in need of more research, as outcomes and effectiveness of different surgical techniques are still heavily debated and opinions on the matter differ a lot between researchers and papers.

This review aims to establish a detailed overview over fetal teratomas, their origin, diagnostics, treatment and follow up. The goal of this research is to provide a summary of the topic and give practical recommendations to healthcare providers who are looking for a structured overview. This review looked at 51 papers on the topic of fetal teratomas containing research from the last decade. It found that due to diagnostics and imaging methods evolving over the past decades and the invention of new surgical techniques massive sacrococcygeal teratomas and other life threatening teratomas can be treated successfully in many cases and are not necessarily a death sentence for the fetus anymore. But due to the infrequent occurrence of fetal teratomas, specialisation can be hard and more research especially on the different surgery methods needs to be carried out.

Keywords

Fetal teratomas, sacrococcygeal teratoma, intrapericardial teratoma, fetal head and neck teratoma, fetal surgery, EXIT Surgery (Ex Utero Intrapartum Treatment)

Introduction

The research that can be found on fetal teratoma is mostly composed of case reports and specific articles on parts of the topic like for example ultrasonography findings and specific treatment options like surgery. A few retrospective studies can be found as well. What is missing from the articles and research is a comprehensive, up to date, overview. This review aims to establish exactly

that: a detailed overview over fetal teratomas, their origin, diagnostics, treatment and follow up. The goal of this research is to provide a summary of the topic and give practical recommendations to healthcare providers who are looking for a structured overview.

Methods

For the collection of data the two databases Pubmed and Google Scholar were used. The last ten years were taken as a time period in which research was accepted with the exception of four sources that date back further. These sources were used for definition purposes. All kinds of studies that reported directly on the case of fetal teratomas or provided additional information were considered as eligible sources.

51 sources were deemed eligible by the author. This included 19 scientific articles, one prospective study, 10 review articles, 5 systematic review articles, two letters to the editors, one casebased review, one population based study, 6 case reports, three excerpts from topic related books, one case control study and one multicenter study. The language for publications was limited to english. Sources were excluded from this review if the publication was not available in english, the source was outdated or the article was not available as a free full text or not available via the access provided by the Vilnius University online library.

To find eligible sources, keywords for searching both databases were used. The terms searched included but are not limited to: fetal teratoma, fetal sacrococcygeal teratoma, fetal teratoma diagnosis, fetal teratoma management, fetal teratoma imagining, fetal teratoma ultrasonography, fetal teratoma follow-up, EXIT to resection, Ex-utero surgery fetal teratoma, parasitic fetuses, fetal head and neck teratoma, intrapericardial teratoma, intracranial teratoma, cervical teratoma.

Literature review

1. Introduction to Fetal Teratomas

Fetal teratomas are generally rare, but are the most common type of fetal tumors found worldwide. The incidence of fetal teratomas is 0.07 to 2.8 per 1000 pregnancies. (1) The word Teratoma was first fabricated by Virchow in 1863. It has its origin in the Greek word “teras”, monster, and means something like “monstrous tumor”.(2,3) Teratomas typically consist of ectoderm, endoderm and

mesoderm, thus all three germ layers that form the embryo during its development. In addition these Teratomas commonly originate from one of the five subtypes of germ cell tumors. (3,4)

Fetal teratomas present mostly with normal karyotypes, though there have been reports of cases in which chromosomal abnormalities were correspondent with certain Teratoma types. (1) They tend to form on the midline of the body, where the most common location for a Teratoma to develop in a fetus is the sacrococcygeal region. Sacrococcygeal teratomas make up 60-80% of teratoma cases found in fetuses. Locations that are otherwise frequent are mediastinum and the head and neck. Less common locations are intracranial, retroperitoneal or pericardial.(1) The phenomenon of Fetus in Fetu is a very rare case were a tissue mass that mirrors the appearance of a twin fetus containing a spine and skeleton is found within the body of the host fetus. There are about 200 reports on this phenomenon in the literature thus far. With the most common location of said tumor being the retroperitoneal region. (3)

The origin of teratomas arising in fetuses is still not completely understood. But there are multiple theories on the development of them. The main three are: one they originate from totipotent cells that come from the migratory path of the Henson's node. This theory could explain the frequent location at the midline as well as the paraxial location of fetal teratomas. Also explaining the amassment of the sacrococcygeal location.

Or two, they are a consequence of incomplete twinning which could tell us why they present in mediastinal, abdominal, intracranial and sacrococcygeal regions. These regions are also the frequent attachment points for conjoined twins.

And three, they come from primitive germ cells that wander from the hindgut to the urogenital edge which could provide the answer to the gonadal and pelvic locations of fetal teratomas. (3)

2. Fetal Sacrococcygeal Teratoma

2.1. Epidemiology

Sacrococcygeal Teratoma has a prevalence of approximately 30.000 to 40.000 to 1 in every birth which makes it the most common congenital tumor. It is more dominant in female fetuses than in male fetuses with a ratio of 3:1. (5) SCTs are sporadic, showing no real familial tendencies except for a family history of twin gestations that can be observed in 10 to 15% of patients. Associated congenital anomalies can be seen in 15-30% of the patients with SCT, with the most frequent

anomalie being of the urogenital system. Here hydronephrosis is very common. This can be explained as a result of the compression to the surrounding organs by the tumor. (6) Causative associations are not found frequently. There is one exception: The Currarino triad. It is a very rare syndrome which presents with a presacral mass, sacral bony defects and anorectal anomalies. Around 40% of the presacral masses found in these patients are Teratomas. This syndrome is autosomal dominant and linked to mutations in the HLXB9 gene. (6)

2.2 Pathogenesis

SCT has its origin in the progenitor node also known as the Hensen's node found on the embryonic progenitor strip. If the Hensen's node persists because of a disorder in the development of the embryo a SCT develops in the sacrococcygeal region. (7)

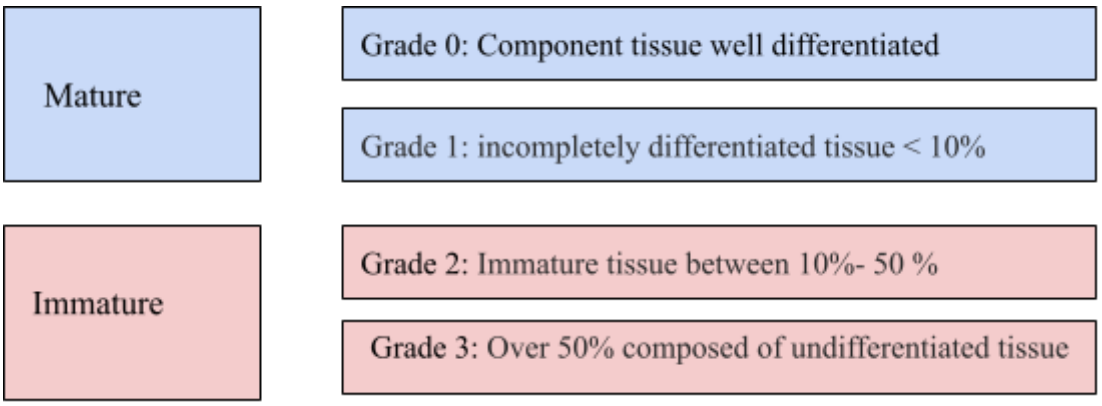
SCTs present as either a tumor in utero or of infancy, sometimes detected by ultrasonography in early pregnancy, as early as 13 weeks of gestation. The most frequently prenatally detected histological subtype is mature SCT. These Tumors are then further classified by the Altman classification system. This system describes and categorizes SCTs on the basis of their location. There are four distinctive types found in this system.

- Type I: Predominantly external with minimal internal components.
- Type II: Approximately equal external and internal components.
- Type III: Predominantly external (pelvic) with external presence.
- Type IV: Entirely internal.

A cohort study done in the UK containing 37 cases of Sacrococcygeal Teratoma found that Altman Type I was the type presenting most often and accounting for 62% of the cases, the second most common Type was Type III with 19%. Type IV SCTs are the least frequent at 6% presentation rate but are often associated with elements of malignancy and are usually detected later in infancy due to their internal location.(1,6,8)

Another useful classification, especially for understanding the tumor's potential in being malignant, is the Gonzalez-Crussi classification system. This system is used to classify teratomas of all kinds based on their degree of immaturity.

Gonzalez-Crussi Classification System



(Fig.1.extracted from "Gonzales-Crussi F. Extragonadal teratomas.") (9)

It is shown that the more immature cells a teratoma contains, the higher is the potential risk of it becoming malignant over the course of a life span. This is seen especially in Grade 2-3 with significant immature neuroectodermal tissue. This histological classification, used to this day, helps in guiding postnatal patient management. (1,9)

2.3 Diagnosis

Fetal sacrococcygeal teratoma is detected in prenatal ultrasound in 25-50% of the cases.(6) And in some cases after the suspicion on US arises, confirmed by magnetic resonance imaging. (7) Whenever SCT is suspected the pregnant patient should always be referred to a specialised clinic with an experienced team. This team should contain a perinatology specialist as well as an pediatric surgeon to ensure both mother and baby get all the resources available during the pregnancy, birth, and afterwards during the follow up period. (10)

In the last few years we can observe a centralisation of perinatology centers that are able to provide care to these types of pregnancies, that are complicated by fetal malformations such as Teratomas, in europe. This centralization leads to an increase in experts who are able to perform highly specialised invasive procedures, that are able to change the natural course of the disease, improve the neonates overall condition or plainly save the fetuses life. (10)

2.3.1 Ultrasonography

The prenatal diagnosis of fetal SCT frequently happens during the regular second trimester anatomical Ultrasonography scan and can be considered the gold standard for SCT diagnosis.(1,11)

Although some cases have been identified as early as the 13th week of gestation. (12) Ultrasonography shows a very high sensitivity and a low false positive rate of only 3.3% in the diagnosis of fetal teratoma. The positive predictive value of ultrasonography is 83,3% and its specificity rate at 96,7 % is also significantly high. (13) In addition it is minimally invasive.

Ultrasonography is of extreme value for the assessment of the tumor's characteristics and its risk stratification. US is particularly helpful for identifying the high risk findings like: the size of the tumor, its vascularity and other associated complications. Because Teratomas are often high in vascularity, three dimensional Doppler ultrasonography can be additionally used to clarify findings.(1) The suspicion for sacrococcygeal teratoma often arises when a complex mass, that is located in the region of the coccyx, is seen on routine prenatal ultrasonography. (3)

As a consequence of the complicated nature of the teratoma, ultrasonography results can vary a lot. Which results in the tumors presenting as cystic, solid cystic and solid mass, and sometimes even with calcified regions, on imaging.(3,7) Doppler US may additionally show eminent features of vessels feeding the tumor.(3) When the lesions are predominantly cystic they can present with little to no vascularity seen by color doppler flow. In other cases when lesions are mostly solid, they present as vascular and can be supplied by large branches of expanded arteries, for example the middle sacral artery. (14)

Sacrococcygeal teratoma increases perinatal mortality and morbidity due to associated complications such as: polyhydramnios, bleeding, cardiovascular complications dystocia or fetal hydrops. Prognosis regarding vascular complications that might arise from the tumor mass, can be made by repeated evaluation of the fetal heart size and Doppler measurements of the fetal cardiac output. Observations of decreased or reversed diastolic flow from the umbilical artery on Doppler US, that are showing competitive “steal” from the Placenta to the sacrococcygeal teratoma are generally a poor prognostic factor. (10,15) Elevated combined cardiac output is often seen on fetal echocardiography. This condition is closely associated with the development of polyhydramnios that might eventually lead to high-output cardiac failure. In the event of tumor hemorrhage, fetal anemia may contribute to elevated cardiac outputs. In turn elevated fetal right heart pressures can cause absent or reversed blood flow in the ductus venosus and worsened tricuspid valvular regurgitation, which can be seen on fetal Doppler US. Placentomegaly, placental edema and maternal mirror syndrome are all closely associated with it and should be closely monitored. Fetal

hydrops in fetuses with sacrococcygeal teratoma is a huge marker for fetal right heart failure and a predicting factor for fetal death. (14)

An important leap into the direction of reducing the rate of fetal death is the identification of causes for it. One crucial tool in prenatal diagnosis using US, is the second-trimester uterine arteries pulsatility Index (PI), which helps in giving insights into the possible etiology of stillbirths. This Index shows placental pathology and is used to find potential issues with the placenta like: placental infarction, placental hypoplasia, distal villous hypoplasia, accelerated villous maturation and retroplacental hematoma.(10,16)

In general it can be said that prenatal US is the best method for the early detection and diagnosis of fetal sacrococcygeal teratoma and is used as the main tool for screening in pregnancy. US is able to provide the shape, size, location, internal echo as well as the blood supply and the SCTs relationship with the surrounding tissues. Moreover the US can show the presence of risk factors and complications such as cardiac dysfunction, abnormal amniotic fluid volume, fetal edema and placental thickening. In spite of that there are some limitations to ultrasonography. The US itself shows poor visual field as well as a weak soft tissue echo contrast. These are both heavily influenced by the US machine operators technique and skill level. In addition to that abdominal fatty tissue, the amniotic fluid volume and the fetal position all play a significant role in the results. Therefore, in cases that show lack of clarity the combination of ultrasonography and MRI use is recommended. (7)

2.3.2 Magnetic Resonance Imaging (MRI)

In cases where an abdominal or sacrococcygeal mass is found on US, MRI can be used for further examination. It can provide valuable insights not only on diagnostics but on treatment recommendations, counseling and delivery planning. MRI provides a large vision field and high resolution soft tissue imaging which can be the point of failure for ultrasonography sometimes. In addition to that it is generally unaffected by fetal position, which can cause visualization problems on US in the later pregnancy stages. Having detailed information on the fetal position can give insights on the localization and qualitative diagnosis of the tumor. Furthermore MRI provides high quality imaging even with insufficient amniotic fluid. Some studies show that MRI can produce more information than US. (7,13)

In recent years, the additional use of MRI in SCT diagnosis has shown that it is able to more accurately describe the intrapelvic expansion and compression of the organs surrounding the SCT lesion. A study that looked into the cases of 11 fetuses presenting with fetal SCTs that were diagnosed in utero, showed that MRI provides better visualization of tumor extension, it accurately describes the involvement of the colon in the lesion, and displays other associated complications better in comparison to ultrasonography. Nonetheless there was always a good overall agreement between the two methods. (1)

The MRI scans can be performed with the pregnant woman lying either on their back facing up or on the left side while advancing their foot. It should be refrained from the use of sedatives and contrast agents. Holding the breath during the scan also is not necessary. (13)

Currently, the biggest concern, regarding patient and fetal safety, in MRI use, is the process of deposition of energy in the body in the way of heat. This is calculated by the specific absorption ratio (SAR) and measured in watts per kilogram (W/kg). Animal studies have shown that a rise in the mothers body temperature of 2-2,5°C for a minimum of 30-60 min can cause fetal harm. Which is why it is recommended to not exceed SAR of 4 W/kg. This frequency is not associated with any harm to the fetus. Contrast agents used for general MRI scans, like Gadolinium based contrast agents are classified as C agents by the United States Food and Drug Administration, which means that they showed some adverse effects in animals but there are no sufficient human studies done. They should only be used in the case where the potential benefits outweigh the risks.(17)

Scanning sequences that are most suitable are single-shot fast spin echo (SSFSE), balanced fast-field echo (BFFE) and T1-weighted imaging (T1WI). SSFSE sequences are used to scan the transverse, coronal and sagittal sections of the fetal abdomen and chest. The main focus here is the size, shape and the signal characteristics of the lesion. The relationship the tumor has with the surrounding tissue and also the relation of the SCT with the fetuses vertebral lumen and vertebral body can be seen very well on SSFSE sequence. Sagittal sections of T1WI can be used to look for the position of the tumor in relation to the fetal rectum. SSFSE sequence scans also provide valuable insight into brain structural malformations when being used for fetal brain cross-section. BFFE scans are mainly used for fetal heart cross sections to rule out obvious cardiac macrovascular malformations.(13)

On MRI sacrococcygeal teratoma is usually presented with cystic or confounding signal lesions. Oftentimes they are related to the caudal vertebra but there is no connection between the tumor and

the spinal lumen and the conus medullaris has not been influenced. T1WI sequence was used in a study that analyzed the MRI data of 60 cases of abdominal or sacrococcygeal masses to show that in Type II and Type III SCTs the rectum was compressed forward in front of the lesion. Complications such as ureteral compression by the tumor, resulting in hydronephrosis, secondary fetal edema and peritoneal effusion can be seen on MRI sequencing. Severe hydronephrosis could lead to necrosis and calcification of the kidney parenchyma. (13)

The earlier and the more accurate a fetal tumor such as SCT can be diagnosed the better are the possibilities for pregnancy management and delivery planning. MRI plays an important role in the further diagnostics and prognosis of SCTs. Depending on the location of the lesion, a sensible differential diagnosis can be made. (18) In the study performed by Li et.al, the MRI diagnosis done prenatally and the follow up diagnosis were identical in 51 cases, which showed an accuracy of 98.08%. (13)

When comparing ultrasonography diagnostic accuracy with MRI accuracy only 75 % of cases were correctly diagnosed by prenatal ultrasonography. Among the left over 25% no definite diagnosis could be obtained and in 11,5% of the cases intraperitoneal mixed echo or presacral mass was not even suggested on US examination. The goal of MRI imaging should be to identify the morphology of the tumor and recognize the possibility for it to extend into the fetal spinal canal. It should also supply evidence of tumor mass effect on bowel or bladder that might be leading to obstruction and consequently to hydronephrosis. (13)

Nevertheless there are some downsides to the usage of MRI as a standard diagnostic tool. There are only little records with small sample sizes that are describing the use of MRI for the diagnostics of fetal SCTs. This complicates making general findings and recommendations on the use of MRI in the diagnosis of fetal sacrococcygeal teratomas. Helpful possible prognostic factors and other factors influencing the prognosis through follow up might still need to be discovered or are in need of further investigation. (13)

3. Complications

Sacrococcygeal teratoma presents with a lot of different complications. These complications will be discussed in depth in this part of the article.

Complications that come together hand in hand in SCT are hydrops fetalis, mirror syndrome and preeclampsia. Fetal hydrops can be explained as an extreme accumulation of fluids in the soft tissue and body cavities of the fetus. It is diagnosed if two or more abnormal pathologic accumulations of fluid are found on fetal US imagining. These collections of fluid can include pericardial effusions, Pleural effusions, ascites and generalized skin edema where skin thickness is over 5mm. Associated findings include placental edema and polyhydramnios. (19)

Mirror syndrome, in some literature called Ballantyne syndrome, is a rare condition that can be found in connection to SCT. It is characterized by hydrops fetalis, placental edema and maternal edema. It got its name because the maternal edema "mirrors" the edema of the fetus with hydrops. The pathogenesis of mirror syndrome is not fully understood to this day, but it seems to be closely related to preeclampsia in the way that trophoblastic damage and maternal vascular endothelial dysfunction occur, which then lead to the release of anti-angiogenic factors from the dysfunctional placenta into the maternal circulation.

The differentiation between preeclampsia and mirror syndrome can be a challenge to clinicians as the two present similarly. Maternal hypertension and proteinuria occur in both syndromes but in mirror syndrome the patients typically present with hemodilution and a low hematocrit level as opposed to preeclampsia patients whose blood is usually hemo-concentrated. General symptoms in mirror syndrome include: hemodilution, placentomegaly, maternal edema, placental edema, fetal hydrops, hypoalbuminemia and preeclampsia. (def: edema, hypertension, abnormal liver function tests, proteinuria). (10,20,21)

Other complications arising from SCT is the risk of dystocia, which is defined as the abnormal prolongation of labour. (22) This may be the case if during birth, the tumor obstructs the birth canal, due to its size. For this reason it is recommended that all SCTs over 5 cm in size should be delivered by cesarean section. (10)

Bleeding can occur due to similar reasons, during labour or in utero, if the tumor size increases so much that the tumor ruptures. (14) This hemorrhaging is a complication that is sometimes overlooked but has a relatively high mortality of 3.8% in neonates. That is why strategies to control tumor hemorrhage like intrauterine interventions and ligation of the median sacral artery before tumor resection should be implemented. (23)

Increased fetal heart to chest ratio and the growth rate of the SCT are linked to fetal cardiac failure due to high cardiac output. This is owing to the fact that the tumor is rapidly growing and supplied with a lot of the fetal blood volume. This is then causing a shift in blood volume that gets increasingly harder for the fetal cardiac system to tolerate. (7)

Lastly, one of the most common complications of fetal SCT is polyhydramnios. (7) Polyhydramnios refers to a pathological condition that is described by an excess of amniotic fluid and characterized by higher fetal and maternal risk for morbidity and mortality. (24) It develops when the process of amniotic fluid volume regulation is disturbed. The most common pathology mechanisms are: impaired swallowing by the fetus, urine production and gastrointestinal obstruction. All of the things above can occur during fetal teratoma development.

The diagnosis should be done via ultrasonography with the healthcare provider measuring either the single deepest pocket or the amniotic fluid index. If SDP exceeds 8cm or AFI is greater than 24cm, polyhydramnios can be diagnosed. Depending on the measurement results it is then classified as mild, moderate or severe.(24)

There are two main ways that cause polyhydramnios in fetal teratoma. The first being decreased swallowing of amniotic fluids by the fetus due to obstruction of the neck in case of a teratoma in the cervical area. A lesion in this area can lead to a crushed esophageal lumen from external compression and therefore leading to polyhydramnios. (3,24)
The second is a surplus in fetal urine production. This is often caused by gestational diabetes but in the case of SCT is caused by the high output cardiac failure, like arteriovenous shunting, that SCT is often associated with.

Polyhydramnios is associated with many risks for mother and child. A prominent one is non-engaged fetal vertex as this may lead to umbilical cord prolapse after membrane rupture, labor dystocia and fetal malpresentation. Additionally, if the uterine overdistension that is caused by high fluid volume gets rapidly restored to its normal size, after rupture of the amniotic membranes, the risk for placental abruption increases. Comparably the chronic overdistension of uterine arteries can lead to uterine atony and therefore postpartum hemorrhage. Also the risk for shoulder dystocia is significantly higher in polyhydramnios.

If underlying pathology like SCT is present the risk for various potential complications increases. A large cohort study showed the presence of major congenital anomalies to be 8%, 12%, and 31% in patients with mild, moderate and severe polyhydramnios. (24)
Polyhydramnios generally increases the risk for preterm rupture of membranes and preterm delivery.(14)

The opposite effect to polyhydramnios could happen if the SCT lesion obstructs the urinary tract. The obstruction leads to bilateral hydronephrosis and/or bladder outlet obstruction which in turn causes oligohydramnios (reduced amniotic fluid) and sometimes even Potter's sequence. (25) Potter's syndrome is a rare disorder that ends in renal failure and is nearly always fatal for the fetus or neonate. Potter's sequence is described as the distinct physical appearance that is caused by the pressure in utero that arises from oligohydramnios. (26)

4. Prognostic factors

The Progress in fetal imaging and interventions that happened over the last decades leads to an ever growing need for prognostic factors that can be used to guide clinical providers and assist in determining if higher level care and fetal interventions or expectant management are reasonable in cases of fetal SCT. (5) The prognosis for neonatal sacrococcygeal teratoma is normally good with the mortality being less than 5%. (14) This stands in contrast to prenatally diagnosed SCT where mortality rates range between 30% and 50%. (5)

Usually found at 20-24 weeks during ultrasonography screening for deformity, there seem to be a few factors, like: tumor growth rate, morphology, vascularity and polyhydramnios that can help predict SCT outcome. (5,7)

4.1 Tumor Growth Rate

Particularly large, solid tumors which are highly vascularized and grow at a rapid rate have been found to be associated with poor fetal outcome. A study done by Rodriguez et al. showed the tumor volume to fetal weight ratio (TFR) evaluated before 24 weeks is a predictive factor for poor outcome. (5)

TFR is calculated by dividing the tumor volume by the estimated fetal weight. The tumor volume should be calculated by using the biggest tumor length, width, and depth to get a prolate spheroid and estimated fetal weight can be calculated by for example, the Hadlock formula. (5,27) A study done by Akinkuotu et al. showed that TFR higher than 0.12 before 24 weeks of gestation predicted a poor fetal prognosis with a sensitivity, which is defined as the probability of a positive test result given the presence of disease (28), of 91.7%, a specificity that is defined as the probability of a negative test result given absence of disease (28), of 76,2% a positive predictive value, defined as the probability of the presence of disease given a positive test result (28), of 86.8% and a negative predictive value defined as the probability of the absence of disease given a negative test result (28), of 84,2%. (5)

These and results from other studies show that TFR is an important indicator for early screening of high risk fetuses. (7) It is a simple tool to use for triaging fetuses presenting with SCT. TFR can be calculated and used in most clinical settings since it uses measures from fetal ultrasonography. It should therefore be integrated in routine obstetric evaluation of fetuses with SCT.

Tumor growth velocity generally seems to be associated with poor outcome independently in contrast to other factors. Here the best predictive cut off of tumor growth velocity seems to be 7mm growth per week, with a sensitivity of 88 and specificity of 77%. (25)

A study performed by Zhong et al. concluded that mortality correlates with gestational age, and that the earlier the diagnosis of SCT was made the poorer was the prognosis. (7) This seems to be also linked to the growth rate of the tumor since the bigger a tumor is the easier and earlier it can be detected on US. (5)

4.2 Tumor Morphology

Solid tumors generally have a worse outcome prediction than cystic ones. In this context Shue et al. found that tumors that were mostly solid before 32 weeks of gestation had a worse outcome. In addition to this other studies have found that it is predictive of mortality and high-output cardiac failure. The reason for this being that tumors that are mostly solid usually are more vascular and cause more shunting of blood away from the placenta and to the tumor when it grows. (5)

Akinkuotu et al. found that tumors that were over 50% solid in composition had a worse prognosis in comparison to patients with tumors that were less than 50% solid. In fact the risk was 7 times higher in the group of patients with over 50% solid tumor composition. (5)
Zheng et al. found that solid tumors with good blood supply that were fast growing were mostly immature tumors. The cystic tumors on the other hand were all mature teratomas. (7)

4.3 Tumor Vascularity

Highly vascularized tumors are also associated with poorer disease outcomes in contrast to less vascularized SCTs. (7) This is because they have high risk for "vascular steal" and intrauterine hemorrhage associated with cardiac failure and hydrops. (3)
Hydrops itself is a poor prognosis factor as fetuses with hydrops have a 3.5 fold greater risk than those without. (5,18) Therefore Fetal SCTs should be closely monitored for the development of hydrops. (5)

Other poor predictive factors for cardiac dysfunction and anemia in fetal SCT are abnormal ductus venosus waveforms and fetal hepatomegaly and should therefore be closely monitored to help guide protocols for interventions. (12,29) Fetal edema is also one of those factors. It can develop from arteriovenous shunts or the tumor hemorrhage and leads to high cardiac output heart failure, indicating a poor prognosis. (7)

4.4 Alpha-fetoprotein (AFP)

Alpha- fetoprotein is the most used serum marker to help with the diagnosis and follow up of teratomas. The biggest source of AFP is the fetal liver, nevertheless the yolk sac synthesizes AFP as well, in the early stages of fetal development. AFP is found during the whole pregnancy and it is a good marker for embryonal and yolk sac derived tumors. The absolute level of serum AFP may give insights into the degree of initial malignancy. Postpartum AFP is crucial in long term follow up and tumor recurrence measurement. (3) Immature teratomas containing yolk sac or other embryonic contents have shown to secrete AFP into the blood, thus leading to an increase in maternal serum AFP. This means that the maternal serum AFP has the potential to be used as an auxiliary index for non invasive prenatal assessment of fetal SCT. (7) Nonetheless should the interpretation of serum

AFP be handled cautiously, since in neonates and infants serum AFP is usually elevated due to its production in the fetal liver.(6)

5. Clinical prenatal management

Prenatal management is crucial to decrease the rate of secondary complications like hydrops, cardiac failure and preterm delivery in fetal sacrococcygeal teratoma. (18) That is why it is recommended to closely monitor patients using recurrent fetal ultrasonography appointments. During these appointments monitoring of tumor growth, amniotic fluid volume, placental thickness and signs of hydrops are important to look out for. A doppler ultrasound should be used on solid tumor lesions to identify blood flow and vascular lesions which can be used as indicators for cardiac function. To accurately detect a high output cardiac state before the onset of hydrops inferior vena cava dilation, flow velocity, blood flow in the middle arteries of the fetal brain and combined ventricular output should be measured. (1,7,14)

Tumors that are over 4 cm in size at around week 20 of gestation should be closely monitored by weekly scans measuring their size, morphology, and vascularity. Growth rates greater than 8 mm/week show a greater risk of adverse outcome, and if combined with polyhydramnios, placentomegaly, cardiac failure or hydrops fetalis, delivery should be considered. (30)

Important to consider during regular patient follow ups is also the possibility of fetal anemia. The increased strain on the fetus due to the high cardiac output that is needed to supply the tumor with blood can be hemodynamically dangerous for the fetus. The increased blood supply to the tumor and the risk for hemorrhage may lead to this anemia. Even mild anemia paired with this increased demand can lead to heart failure, eventually hydrops and maybe even fetal death.

If the middle cerebral artery peak systolic velocity is increased greater than 1.5 multiples of the median on Doppler Ultrasonography, moderate to severe anemia can be suspected. In order to get diagnosis confirmation, percutaneous umbilical blood sampling should be done under the guidance of ultrasonography.

In case severe fetal anemia is detected, intrauterine transfusions are the treatment of choice. Here packed red blood cells should be transfused directly into the umbilical vein, under constant

ultrasound surveillance. The goal of this treatment is to stabilize the hematocrit and help with oxygen delivery to the fetus in order to stabilize the fetus and get a better fetal outcome. In some cases the intrauterine transfusion can be done not only containing red blood cells but also platelets for more effective case management because it addresses secondary coagulopathy seen in SCT. Additionally the approach of targeting the vessels feeding the lesion is supposed to reduce blood flow to the tumor, minimizing the risk of hemorrhage and therefore reduce hydrops and anemia related complications. (1)

Other prognosis factors like tumor size >10 cm, rupture, the amount of solidity of the tumor, increased vascularity, growth rate, TFR etc. that were mentioned extensively above should all be considered and can be useful during management of pregnancy with SCT but it is important to use the specific sonographic and echocardiographic findings of each individual fetus for the prognosis,treatment and follow up.(14)

5.1 Guide for decision on delivery

When thinking about delivery in SCT, vaginal delivery should always be the option that is thought about first since it is associated with lower maternal morbidity and mortality. (10) It is generally recommended in cases with a tumor size under 5 cm. (7) Cesarean delivery is indicated when there is a risk of bleeding or dystocia as it is often the case in SCT. (10)

The delivery mode should depend on the maternal fetal complications present in the pregnancy, growth pattern, maternal birth canal conditions, tumor size and fetal orientation. The gestational week at which the fetus is delivered matters as well for prognosis. If the fetal or maternal abnormalities are not that obvious, delivery at full term is possible. In the event of fetal presentation with edema, maternal mirror syndrome, fetal cardiac dysfunction etc. delivery should be initiated as soon as possible. (7)

If a high risk fetus is over 28 weeks, after the application of maternal steroids to accelerate lung maturation, elective early delivery could be considered. If the gestational week is earlier than 28 weeks, open fetal surgery could be done if high output cardiac failure develops in the fetus. If

complete removal of the lesion is not possible partial removal can aid in decreasing the tumor vascular shunt and help restore cardiac output. (3)

Often in cases of small isolated SCTs where nothing else complicates the pregnancy, elective cesarean delivery after 36 weeks of gestation is chosen to minimize the risk of complications that could occur during vaginal delivery like obstructed labor or tumor hemorrhage.(1) The Incision that has been invented to use, to avoid rupture of the tumor during delivery, is a vertical incision of the upper abdominal wall and then a inverted T-shaped incision for the uterine wall. (7)

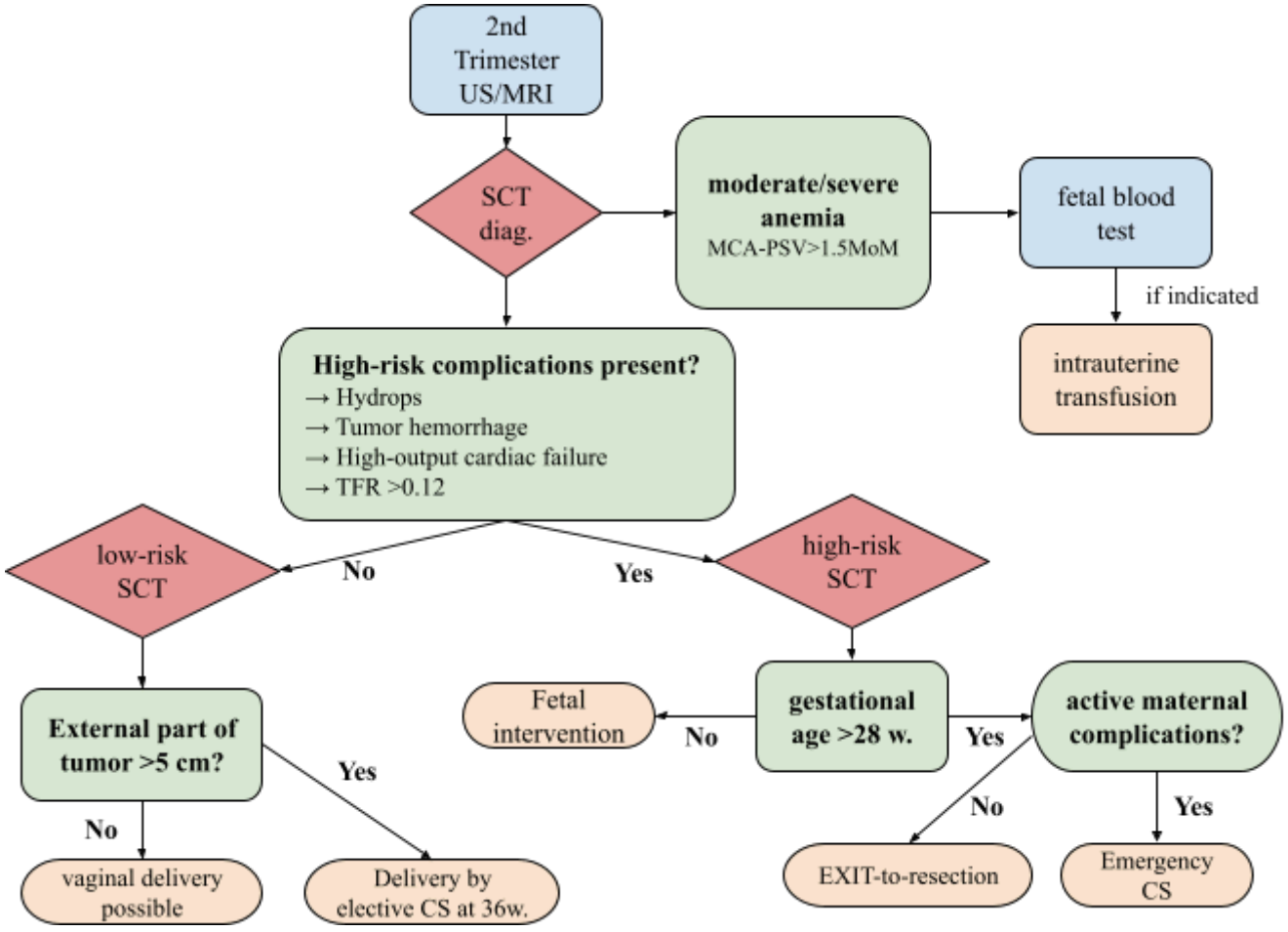


Fig. 2: Algorithm for the management of fetal SCTs extracted from Abiad et al. (US= Ultrasonography, MRI= Magnetic resonance imaging, diag.= diagnosis, MCA-PSV= middle cerebral artery-peak systolic velocity, TFR= Tumor-volume-to-fetal-ratio. CS= Cesarean Section) (1)

5.2 Parental counseling in cases of SCTs

After the first diagnosis of SCT is done by prenatal US or MRI the parents often require prenatal counseling. This could be done by the MRI experts, a professional consultant or any other physician responsible for the care of the expectant mother. It is important for a full understanding of the disease prognosis and for the decision making of the parents. (13,31)

No matter the severity of the SCT, receiving the diagnosis can be traumatic for the expectant parents. It is important that the provider who is counseling, knows the gestational age of the patient to be able to counsel the patient on all her options like termination or fetal surgical intervention. Because the patient usually has seen mostly her obstetrician and maybe a perinatologist up to this point in her pregnancy it is important to know the names of these doctors and at least the basic pregnancy history in order to be able to establish the patients trust. The provider should have as much information on the case they are counseling as possible beforehand, but during the consultation should also take the time to gather a complete history and should always introduce themselves and the role they have in the counseling to the patient. Try to get to meet the family members and friends accompanying the patient as they often have immense emotional value to the patient and can help with further trust building.

Only after getting to know the patient and her complete medical history should you check in with her understanding about the diagnosis. Some patients may already be well informed while others might only have limited or even incorrect information. Using this time to get an overview of the patient's education, beliefs, and anxiety level can be helpful.
Whether the conversation is 5 or 30 min long is not as important on the emotional outcome as the way the information is delivered. Therefore it is important to be compassionate, honest and to maintain integrity. So any healthcare provider delivering the information should take the time to have a focused and compassionate conversion with the patient.

Because patients will probably still have some level of uncertainty after leaving the meeting, it is important to provide the patient with clinical information that is understandable for them in the form of information sheets and pictures. In addition, provide them with materials on perinatal loss and specifically written for parents and other emotional support resources such as individual counseling/ therapy opportunities and emotional support groups. Although patients probably will

not use all resources provided to them, it is important because it may give a sense of control over an otherwise pretty uncontrollable situation. (32)

5.3 Termination of Pregnancy in SCT

Termination of pregnancy is recommended in cases of SCTs that are considered to be immature with rapid growth rates (<150 cm3/week) SCT with abundant blood supply to the tumor, fetal edema, chromosomal abnormalities, other concomitant malformations or SCTs with locations affecting fetal growth. (7) The timing of termination should always be decided with full consultation with the pregnant patient and her family. (7) All families should be informed about the option of termination of pregnancy and it is important that families do not feel judged by the health care team during their decision making process. It is important to provide the patient with detailed information on the facilities and clinicians in their area who provide pregnancy termination as well as laws and regulations surrounding it. If the family wants additional genetic testing or autopsy after the termination, their options and the process needs to be explained as well. (32)

6. Treatment

Because of its low incidence fetal SCT treatment is still very experimental. There are no guidelines and expert consensus is small. Individualized treatment based on the maternal and fetal condition and patients wishes is the norm. It can be symptomatic treatment, fetal intrauterine treatment, termination of pregnancy or neonatal treatment. If there are cardiac abnormalities and signs of fetal edema present before the fetus reaches viable gestational age, intrauterine therapy might be considered. This includes: radio-frequency ablation, alcohol sclerosis, vascular embolization and even open fetal surgery. All of these therapies aim to prevent arterial venous shunting and reduce tumor size or even remove it completely. Nevertheless procedures like these are not without risks and can result in complications like intrauterine stillbirth, maternal injury or preterm delivery. Successful cases of intrauterine treatment are still rare so it is important to communicate clearly with the pregnant patient to inform them of all adverse possibilities. (7)

6.1 Prenatal surgery

In case the SCT condition progresses rapidly before 28 weeks of gestation immediate fetal intervention is recommended (10). This includes: EXIT to resection, Cesarean-Section-to-Immediate-Resection or open fetal surgery.(1) In cases of severe hydronephrosis intrauterine surgery can be necessary to prevent secondary fetal edema and severe renal necrosis. Fetuses with hydrops fetalis had a survival rate of 38% when they had an intervention done vs 9% survival rate in the group that had no intervention.(13)

6.1.1 Ex Utero Intrapartum Treatment Surgery (EXIT)

The Exit procedure is a highly controlled method of delivery which uses deep anesthesia and uterine relaxation to keep placental circulation going. This is done so that the infant can still get supplied with oxygen while also interventionally securing the neonates airways prior to delivery to minimize the risk of hypoxia. In cases of SCT it is used to deliver fetuses with severe cardiopulmonary insufficiency. (33)
It is important to minimize uterine tone without compromising perfusion to the fetus therefore anesthesia considerations are critical. At the beginning of the procedure the mother is in a lateral decubitus position and an extended Pfannenstiel incision is done to expose the uterus. Ultrasonography is used to see the placental borders to find the ideal hysterotomy side. Then the hysterotomy is done using an uterine stapler that fuses the amniotic membranes to the uterine wall. When the fetus is exposed, fetal anesthesia is administered and laryngoscopy to secure fetal airways is performed. Afterwards surgical resection of the teratoma is done and upon completion the umbilical cord is cut and the fetus is delivered.(3,33)

A Case in which EXIT strategy for SCT was successful is described by Ding et al. The neonate survived and was able to be discharged after 19 days in the hospital.(34) Nonetheless there are challenges for the treatment of SCTs with EXIT surgery. It should only be attempted if all of the following conditions apply: singleton pregnancy, normal karyotype, no other malformations, evidence of high output cardiac failure, gestational age over 30 weeks, Altman Type I or II and no maternal risks or contraindications for anaesthesia. Complications include preterm birth, premature ruptures of membranes and infection after surgery, tumor hemorrhage and asphyxia due to failed intubation.(34)

6.1.2 Open fetal surgery

Open fetal surgery is a surgery performed with the goal to be able to maintain placental perfusion and continue the pregnancy afterwards for as long as possible. The procedure is similar to the EXIT procedure. The abdomen is opened via a low transverse incision and the same specialized uterine staplers are used. The fetus is then put in the necessary surgical position and the removal of the SCT is performed. During the whole procedure the uterus is continuously perfused with warmed lactated Ringers solution to mimic amniotic fluid and prevent uterine contraction and after the uterus is closed it gets infused with lactated Ringer solution containing antibiotics.

After this surgery maternal and fetal surveillance is very important and tocolysis should be done continually. Delivery is normally planned at around 36 weeks of gestation via Cesarean Section. The most common complication is preterm labor with a mean delivery age of 34 weeks. Other complications of this procedure include: maternal non cardiogenic pulmonary edema, thought to be caused by vasoactive agents released by the disrupted myometrium, amniotic fluid leaks and chorioamniotic separation. (33) Open surgery is contraindicated in extreme placentomegaly, serious cervical shortening and Altman type III and IV tumor types. (1)

6.1.3 Fetoscopic surgery

Recently after the rise of video assisted laparoscopy fetoscopic surgery has become an alternative to open fetal surgery with the hope to reduce maternal morbidity and the incidence of preterm labor. It uses small laparotomy incisions in both abdominal wall and uterus. Trocars are placed into the amniotic cavity and a flexible fetoscope is placed into the amniotic cavity. After the procedure is done all exit sights are closed. In a study involving 187 women undergoing intrauterine fetal intervention, fetoscopic surgery showed decreased maternal morbidity in terms of length of hospital stay, decreased need for transfusions and fewer ICU stays in comparison to open fetal surgery. Nevertheless there was no significant difference in preterm labor incidence. It was shown that the risk for chorioamniotic separation is actually increased in fetoscopic surgery. Despite that it is a promising method for intrauterine fetal intervention.(33)

6.1.4 Minimal invasive surgery

Additionally to classic surgical resection there are other more minimal invasive methods for the treatment of SCTs. Some of these methods include radio-frequency thermal ablation (RFA) (6,14), serial laser coagulation (35), thermocoagulation or coil/alcohol embolization. (14) These methods have been developed to rescue complicated cases with large SCTs or decrease surgical bleeding in neonates.

If the tumor is largely cystic, aspiration in utero can prevent preterm labor or labor dystocia. Ablation techniques are still under development to reverse fetal heart failure but they generally seem to have a similar mortality to classic surgical approaches.(6) These procedures are all generally performed under US control are not as invasive and avoid hysterotomy but the indications are often incomplete and published results are poor.

Specifically procedures involving coagulation might bear more risks than first expected. It is very difficult to coagulate the complete venous and lymphatic drainage of the SCT. Furthermore ischemia and necrosis may lead to the release of intracellular potassium and cytokines into the fetal bloodstream potentially causing more decompensation or early delivery. Potential risk of tumor hemorrhage and thermal damage to surrounding structures and with that permanent disability also need to be taken into consideration.(14) That is why parental counseling on the risk and outcomes of these procedures is of utmost importance.(14)

A systematic review of Intrauterine Interventions in fetal SCT done by Konno et al. showed no significant difference between open surgery and percutaneous intervention with a total survival of 56.2% in open surgery and 45.8 % in percutaneous intervention.(36)

A new approach proposed by Fulati et al. involves a smart shape polymeric string that is applied to the SCT via fetoscopic surgery and that is then used to restrict blood flow to the tumor and therefore arrests its growth. The material of the string is a non toxic biodegradable synthetic polyester with good shape memory properties. This approach could be promising but has not been tested extensively yet and therefore needs more research done before it can be recommended.(37)

6.2 Postnatal surgery

For SCT that can be delivered without the need of intrauterine fetal intervention it is usually enough to remove the SCT postnatally. Because SCT can become malignant resection is planned as soon as possible to decrease the risk.(6) Chemotherapy is usually used only as a last resort and survival rates are up to 100% even for those with malignant disease.(14) The surgery can be done openly or laparoscopically and involves complete removal of the tumor and coccyx. (3,10) Altman types I and II, which are present in most cases, can be operated via the sacral approach only. Altman types III that are large and have external and internal parts often need a combined sacral and abdominal approach. Tumors that only contain an intrapelvic part can be removed by laparoscopy.(6)
When the tumor's extent is notably intra pelvic or abdominal, surgery can be challenging and the risk for injuries or residual tumor parts increases. Long term bladder or bowel dysfunction can be caused by injury to adjacent structures such as the ureter, bladder, pre-sacral nerves or rectum. (3)

The most common complication arising postoperatively is wound infection and dehiscence. A Cause for this could be the close proximity of the anus to the wound. Rates of infection differ greatly in literature with rates from 7.3% to even 90%. (38)

In order to prevent hemorrhagic mortality Kremer et al. suggests waiting for surgical resection until a more hemodynamic and respiratory stable situation is achieved. This approach is not free of risk as preceding bleeding is often the cause for bad hemodynamic situations leading to a dangerous cycle. (23)

6.3 Fetal anesthesia

There seems to be an ongoing debate whether a fetus is able to feel pain during fetal surgery or not but recent discoveries like an increase of cortisol and adrenaline levels or the development of bradycardia following a painful stimuli in fetuses between 16-25 weeks of gestation show a pain reaction during prenatal life and therefore call for effective fetal anaesthesia. (39)
A possible approach to fetal anaesthesia is proposed by Choudhury et al. They followed standard anaesthesia technique by pre-oxygenating and pre-medicating the fetus with 1 μg/kg fentanyl. Then tracheal intubation was performed using injection thiopentone 4–5 mg/kg i.v. and muscle relaxation with injection rocuronium 0.9 mg/kg i.v. During the duration of the surgery the anesthesia was kept up with sevoflurane (0.2–2%) in N2O:O2 at 60:40 and top ups of rocuronium. If blood loss would

be exceeding the maximum allowable blood loss it could be replaced by packed red blood cells (10–15 ml/kg). After the surgical procedure is finished, i.v paracetamol can be given for pain relief as intraoperatively caudal block is often impossible to give due to the sacral lesion. (40)

7. Clinical postnatal management & follow up

The most important and therefore most used serum marker for diagnosis and follow up of fetal teratomas is serum alpha-fetoprotein. AFP is mostly synthesized in the fetal liver but the yolk sac also plays a role in it. AFP is therefore a good marker for embryonal and yolk sac derived tumors such as SCT. Following AFP levels can be used to track recurrence after surgical removal.(3) The AFP levels should normalize in months after birth. If they exceed the normal levels it could be a sign of recurrence and malignancy. (41)
AFP levels can therefore also aid in seeing the effectiveness of treatment. Reasons for tumor recurrence can be tumor spillage, immature/malignant histology (yolk sac tumor and/ or embryonal carcinoma), or incomplete resection. (42) Mature teratoma has a recurrence of 10%, immature has a recurrence of 33% and malignant teratoma a recurrence of 18%. (41) Because all kinds of teratomas have a risk for recurrence they should all be monitored. (7) And even if immature SCT histology is a risk factor for recurrence it is not recommended to generally apply postoperative chemotherapy for prevention of recurrence. (6) One way to minimize the risk of recurrence is by removing the coccyx during SCT removal surgery. (6)
Oncologic follow up of SCT patients in 3 month intervals for at least 3 years is recommended. (6,41) During Follow up a digital rectal exam and serum AFP checks should be done. Additionally if elevated AFP levels or suspicious physical findings are observed an MRI or computer tomography exam should be done. In Germany routine imaging is performed every 3 months for the first year and then from the second year every 6 months. Longer surveillance can be considered, as very late recurrences, even after 5-15 years have been seen. (6)
For recurrent SCT chemotherapy is used as a treatment strategy. There is no one chemotherapeutic regimen that fits all recurrent SCT cases but research has shown that a regimen including platinum compound has good prognosis for achieving stable remission. The 5 year overall survival for recurrent malignant SCT was 42%. (6)

Another thing that needs to be considered regarding follow up of cases with SCT is functional outcome after the surgery. A Study found that urological dysfunction is a problem in 33% of SCT survivors and anorectal sequelae concerns 29% of survivors. Common consequences of SCT are

urinary and fecal incontinence but also constipation, neurogenic bladder and vesicoureteral reflux.(6) These issues with bladder and bowel control are most common in higher Altman classifications. A questionnaire study performed in the Netherlands that asked long term survivors of SCT about these things found that 46% experienced problems with their bowel function, 31% suffered from urinary incontinence and 40% had unacceptable scarring from surgery. Surgery as extensive as needed for SCT in some cases, this early in life, also often leads to sexual dysfunction later in life. (1,6)

Mortality in general for infants with SCT can be split into two groups of causes. The first being the SCT lesion undergoes malignancy and is not caught in time which in turn leads to the death of the infant or the second being hemorrhage of the SCT before or during surgery that leads to the most causes of death in neonates with SCT.(23)

8. Differential Diagnosis

SCTs need to be distinguished from a few other anomalies. The main ones being neural tube defects like: Myelocystocele, cystic limited dorsal myeloschisis, terminal myelocele or meningomyelocele. Myelocystocele usually presents with posteriorly splayed spinal elements and a meningocele. Sacrococcygeal meningomyelocele ist mostly located in the rear of the sacrococcygeal region and contains cerebrospinal fluid cysts that connect with the spinal lumen. Other anomalous masses of spinal dysraphism are usually located higher up at sacrum and coccyx and characterized by specific skin stigmata like hair or a hemangioma over the lesion. They are usually additionally accompanied by neurological deficits like bladder dysfunction and lower extremity weakness.
In Contrast to this, sacrococcygeal teratomas are always located near the coccyx; they often displace the anus posteriorly and form a presacral mass. (1,6,13)

Cloacal malformations also need to be distinguished from SCT lesions. They are rare with reports of 1 in 50.000 t0 1 in 250.000 and occur in female fetuses. They usually present as a repeated uterus and vagina with cystic dilatation. Compression of the ureter that leads to dilatation of it and/or hydronephrosis is more common in cloacal malformations than in SCT. On MRI cloacal malformations present as showing the rectal lumen with a high signal behind the cystic lesion because of the dilated uterus and vagina while in SCTs the rectum is seen before the lumen. (13)

Lastly parasitic fetuses should be differentiated from SCTs. They can be distinguished well on MRI. Parasitic fetuses are framed by a clear water sac and show lesions containing limb bones or a spinal structure and usually show low signal. Teratomas usually present with mixed signals and no limb or spinal structures. Parasitic fetuses can also have blood supply and might increase in size when the fetus grows. It has been shown that in 87.5 % of the time the parasitic fetus was located in the upper left abdomen. (13)

9. Parasitic fetuses

Parasitic fetus also known as Fetus in fetu is an extremely rare congenital anomaly. Its incidence is approximately 1 in 500.000 and less than 200 cases have been reported in history. The pathology is unclear but it is believed that it is connected to abnormal embryonic development where the two embryos are very different in development and growth. The larger continues to develop while the smaller one arrests in growth and attaches to the other. The most common attachment site is the retroperitoneum. (43)
Characteristics are a mass surrounded by a distinct fibrous membrane covered partially or fully in skin that shows grossly anatomically recognizable structures and is supplied by large blood vessels. On US rudimentary organs can be identified. (13)
Parasitic fetuses seem to show a 2:1 male dominance unlike the female dominance for teratomas. The diagnosis is relatively easy as it involves mainly the identification of a spinal structure or limbs.(13)

10. Intrapericardial Teratoma

Intrapericardial teratomas are rare cardiac tumors usually made up of endoderm, mesoderm and neuroectoderm germ layers. They make up around 10% of the mediastinal tumors in pediatric patients. (44,45) It is defined as a teratoma with its origin in the pericardial sac that is covered by parietal pericardium. (46) Intrapericardial teratoma is a rapidly growing tumor that is usually benign but due to its location and growth can lead to massive pericardial effusion and cardiac compression which results in cardiac distress and even hydrops fetalis. This is why mortality is high even though the tumor is usually benign. (44,47)

Diagnosis of intrapericardial teratomas are usually done via Ultrasonography and fetal echocardiography. On US a large irregularly shaped heterogeneous mass that seems to have its

origin outside of the cardiac chambers but from within the pericardial sac lining is seen. This lesion is then often accompanied by pericardial effusion. (46,47)

Other complications arising from intrapericardial teratoma are large tumor size associated with pericardial effusion which in combination can lead to constraint of heart filling, cardiac tamponade, fetal hydrops and death.(46)
Fetal hydrops seems to occur in around 70% of cases of fetal intrapericardial teratoma. Causes for this can be the mass effect of a large tumor or a cardiac tamponade that is caused by a pericardial or in very rare cases a pleural effusion or both.
The prognosis for fetuses who do not develop hydrops during the pregnancy and afterwards undergo postnatal surgery is actually quite good at a little over 90%. Sadly this is not the case for fetuses that develop hydrops during the pregnancy. They seem to have a high risk for poor outcomes and pregnancy interventions should be considered. (47) So far no correlation between hydrops and tumor size has been found. (44)

Neonatal cases of previously undetected intrapericardial teratoma present with respiratory distress, cyanosis, superior vena cava obstruction or cardiac tamponade. In this case intrapericardial teratoma should be suspected and two dimensional echocardiography is still the gold standard tool for diagnosis. MRI can also help with demonstrating the relationship of the lesion to the surrounding tissue. (44)

If a small lesion that is suspicious for being a pericardial teratoma is detected it should be checked up on frequently for size changes and cardiac output changes. It is generally favorable for the fetus if the condition decline is detected before the onset of hydrops. Fetal interventions are much less risky if the fetus is in a stable condition to avoid having to treat the fetus in an unstable, maybe even injured state. (46)
Because Doppler flow abnormalities in this type of teratoma seem to only occur after the onset of hydrops they are not a good predictor of future instability but rather show the current cardiovascular instability and therefore should not be used as treatment indicators. Better indicators for treatment are increase in tumor size, the location of the tumor and abnormally low or declining cardiac output. (46)
Prenatal treatment options for intrapericardial teratoma include: pericardiocentesis which is the aspiration of the pericardial effusion, thoracocentesis the aspiration of a pleural effusion in case its

present, amniodrainage of polyhydramnios, the placement of a pericardial amniotic shunt, laser ablation of the tumor (not very commonly done and not very well researched) or open fetal surgery. The first methods are less invasive and seem to be able to prolong the pregnancy. If the fetus improves after the aspiration of the effusion but then cardiac compromise and the effusion reappears is suggestive for shunt placement. This needs some further research done as it is not known yet if and to what lengths it can increase pregnancy duration.(44,47)
These types of teratomas like all teratomas can have cystic components. Draining of these cysts does not necessarily lead to tamponade relief and does not inhibit rapid tumor growth. The most effective treatment is tumor resection. (46)

Delivery after 28 weeks and then postnatal surgery have a high success rate. They are almost curative and provide immediate symptom relief. It was found that around 90% of intrapericardial teratomas were attached to the aorta or main pulmonary artery and therefore no need for cardiopulmonary bypassing is experienced during surgery. After complete tumor resection no recurrence has been reported.(44)

EXIT to resection surgery can be considered if the tumor size is progressively increasing and cardiac output is declining before the 28 week gestation mark. In order for the surgery to be successful it is important that hydrops has not occurred yet.(46) The added benefit of EXIT to resection as a procedure over delivery and then elective surgery after the neonatal condition has been stabilized is still unclear. (47)

Open fetal surgery should be carefully considered in case of intrapericardial teratoma to see if the benefits actually outweigh the risks. Due to the large hysterotomy the risk for infertility, bleeding, hemorrhage and other potentially maternal life threatening complications need to be considered and mothers should be carefully counseled. (47)

11. Fetal Head and Neck Teratoma

11.1 Intracranial teratomas

Intracranial teratoma are the most common type of prenatally diagnosed congenital brain tumor. They are usually benign and contain mature components of all three germ layers and immature

neuroglial cells. These lesions are normally diagnosed on US at average 27 weeks. MRI is an important tool for tumor morphology and location. On MRI the intracranial Teratoma is seen as a large heterogeneous mass. The characteristic intralesional fat deposits are hard to see on MRI. If the lesion is very heterogeneous the tumor is usually more mature which speaks for a more benign histology. Mature teratomas have more cystic components, calcifications and fat. Immature teratomas tend to be solid and homogenous and show higher rates of malignancy. In addition they tend to grow fast and can develop necrotic foci and hemorrhage. Mostly located in the centre they tend to grow and occupy more than one cranial fossa leading to cerebral tissue destruction.

Sometimes the teratoma grows into the face and through the skull base into the oropharyngeal and neck regions the outcome of this is unfavorable as the tumor can not be removed completely. Differential diagnoses to consider are sublobar heterotopias, craniopharyngiomas and hypothalamic hamartomas. (18)

Substantial intracranial teratomas can cause hydrocephalus, intracranial hemorrhage and fast increasing head size. In rare cases this increase can lead to uterine rupture or even fetal head rupture during delivery. Another complication of intracranial teratomas could be labor dystocia due to the large head in comparison to smaller body size. Just like in SCT high output fetal heart failure and hydrops can complicate the pregnancy. In general survival rates for prenatally diagnosed intracranial teratomas are low at 10%. (18)

For the management of pregnancy, termination can be considered. If the pregnancy is continued medical or surgical delivery options need to be planned by a multidisciplinary team. Decompressing the fetal skull using US guidance might be necessary prior to any form of delivery to ensure maternal safety. Monitoring of the pregnancy via US needs to be done according to the case but at least every four weeks and in some cases even every other day depending on the tumor growth rate. The goal is to get as close as possible to term gestational age. For delivery a cesarean section should be performed with the help of a team of high level neonatology care, plastic surgery, neurosurgery, otolaryngology and neonatal palliative care. (18)

11.2 Cervical teratomas

Cervical teratomas are rare and mostly benign. They have an incidence of 1 in 20.000 to 40.000 live births. Diagnosis is usually done via US and they are, like other teratomas, solid and/or cystic in morphology. (48)

From the first trimester on, it is possible to evaluate the face and neck of the fetus on US. Due to positional changes of the fetus in the third trimester it is recommended to perform the US assessment before the 23rd week of gestation. The appearance of the fetal face changes throughout the pregnancy. Here close attention should be paid to the deposition of fatty tissue especially in the maxillary and buccal regions.(49) 3D Ultrasound can help with visualization of surfaces of the head and neck and during the consultation with the parents. MRI and fetoscopy can also be used for diagnosis.(49)

Complications arising from cervical teratomas are often due to their close proximity to the fetal airways and neck vessels leading to neonatal asphyxia and hypoxia.(48) Other complications arising are similar again to complications found in SCT because they correlate to tumor size and vascularisation. High-output cardiac failure, atrioventricular valve regurgitation, hydrops, increased cardiac pre and afterload are all seen in all fetal teratoma types. (48) In cases of large cervical teratomas lung hyperplasia might occur due to compression of the tumor pressing the lungs into the apices of the chest. (50)

To avoid complications of polyhydramnios it is important to assess the Amniotic Fluid Index (AFI) on every visit. Polyhydramnios is a common complication of cervical teratomas. Due to the tumor compressing the fetal esophagus and trachea, swallowing is impaired. If severe polyhydramnios is developed, that leads to preterm contractions or maternal dyspnea, amnioreduction should be performed.(48,50)

Epignathus is a very rare teratoma that grows in the oral cavity and throat and sometimes projects into the nasal cavity and the anterior cranial fossa. It is usually benign, originating from the sphenoid bone, hard or soft palate, pharynx tongue or mandible. On US it presents as a solid tumor with cystic elements and calcifications. It can grow intracranially and result in hydrocephalus. (49,51)

There are some predictors for fetal airway obstruction. They are: polyhydramnios, big lesion size and teratoma presence. Lazar et al. proposed an additional predicting factor called TEDI (tracheoesophageal displacement index). It is the index of the sum of lateral and ventral displacements of the tracheoesophageal complex using fetal MRI scans. A TEDI of 12mm or more is a positive predictor for airway obstruction. (50)
If airway obstruction is suspected a cesarean section with EXIT procedure, like described above, should be done. A new alternative method to EXIT was described by Cruz-Martinez et al. It is called FETI (fetal endoscopic tracheal intubation). During this procedure a fetal tracheoscopy is done while simultaneously an orotracheal cannula is inserted under US guidance to ensure fetal tracheal permeability before delivery. (50)

Differential diagnosis of fetal head tumors by Ultrasound and color Doppler US

Cervicofacial Tumor	Ultrasound characteristic
Teratoma	**solid, cystic elements & calcification possible, location oral cavity & pharynx**
Cervical solid tumor	good differentiation from surrounding tissue, connected to thyroid, vascularized well
Cystic hygroma	solid, located in tongue and cervical region, if septation present → chromosomal defect
Epulis	solid, poorly vascularized, located in oral vestibule
Hemangioma	good differentiation from surrounding tissue, blood flow on Doppler increased
Myoblastoma	solid, location: thyroid tumor in oral cavity
Vascular malformation	cystic with thin septation, blood flow on Doppler seen

Fig.3 from Zieliński et al. (49)

Discussion

It seems as though no research has been done on the topic of fetal teratoma in the past decade in Lithuania as no articles were found by the author. The research done on the topic of teratomas was generally diverse but there was a definitive majority of research done in the USA. Out of the 51 papers that were reviewed 19 came from the USA with a lot of the research performed at Texas University. European papers in general made up only 14 of the 51 papers. Here the Polish and Italian research stands out in its quantity with Poland publishing four and Italy publishing 3 out of the 51 papers used. China has published 5 out of those 51 papers.
There were also two noticeable peaks in research on the timeline of the past 10 years. One Peak was seen in 2016 when 8 of the 51 papers were published and another peak in publishing was observed in 2022 where 11 of the 51 papers were published.
These observations might highlight the need for more research on the matter, especially in Europe as most of the research is USA derived. The recent peak in publishing could underline this as well, as it may be providing a basis for the possibility of further research.

This review as most of the other publications done on this topic is limited by the low case numbers of fetal teratomas. This leads to few research being published on the matter. New and up to date sources are hard to find and usually are either case reports or review articles. These do not provide the highest standard of research as for example a case control trial would. Having only case reports and small sample sizes could also potentially create a research bias where case reports that ended favourable are getting published. This could lead to a mismatch in the survival rate of surgical procedures done.

The low incidence of fetal teratoma additionally means that the treatment in general is very experimental. There are no guidelines or expert consensus that could lead healthcare providers in their decision making, so the treatment is very individualized and highly dependent on the provider. The provider needs to be able to diagnose and differentiate fetal teratomas and be educated on the next steps and where to send their patients for further care.

Becoming an expert in the treatment of teratoma is also nearly impossible because of its low incidence. The treatment strategies like the different surgery techniques are all highly specialised and require immense skill to be executed in a favorable way which in terms means that treatment

outcome is also extremely dependent on the skill and knowledge of the provider. Treatment should be only provided at highly specialized centers in tertiary care in order to be able to provide the team of specialists needed for the treatment of fetal teratoma.

In addition to it being hard to become an expert in the field expert consensus on the different surgery techniques is not given. Many experts debate on which surgery technique to use and different sources state different opinions on what technique is the best and what technique to never use. For example: one expert might say that EXIT to resection is the best way to deliver and treat sacrococcygeal teratoma, while the other says it is too risky and a normal cesarean section with immediate surgical intervention afterwards should be performed.

On the topic of surgical interventions regarding fetal teratomas there is another problem that arises. As there is not enough research or evidence done to support new or different treatment strategies, new and innovative techniques might not get used as they could be. This might happen due to lack of evidence or simply lack of information. This is why it is important that new cases get published and reported on in order for new information to reach providers all around the world.

Conclusion and practical recommendations

In conclusion it can be said that fetal teratomas are rare but can be dangerous to both mother and child. Prenatal ultrasonography and MRI can be useful in the diagnosis.
Regular follow up with detailed monitoring of tumor blood supply, growth rate, size, and pathology are crucial for risk and outcome assessment. Fetal and maternal complications like: cardiac dysfunction, edema and hydrops, amniotic fluid volume, mirror syndrome etc. that might arise from the disease need to be taken into consideration and treated if needed before a type of delivery is decided on.

Fetal surgery, like intrauterine surgery or EXIT to resection, can be helpful tools in the management of fetal teratoma that can potentially lead to a more favorable outcome. The communication between the mother and the doctor is an important part of the treatment plan as is the specialised healthcare team involved in the treatment of fetal teratoma. The expertise and skill of the doctor is closely related to the patient's outcome. Because of low incidence numbers research on this topic is still not as abundant as it should be and more research is required.

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